



Diagnosis and Management of Cirrhotic Ascites

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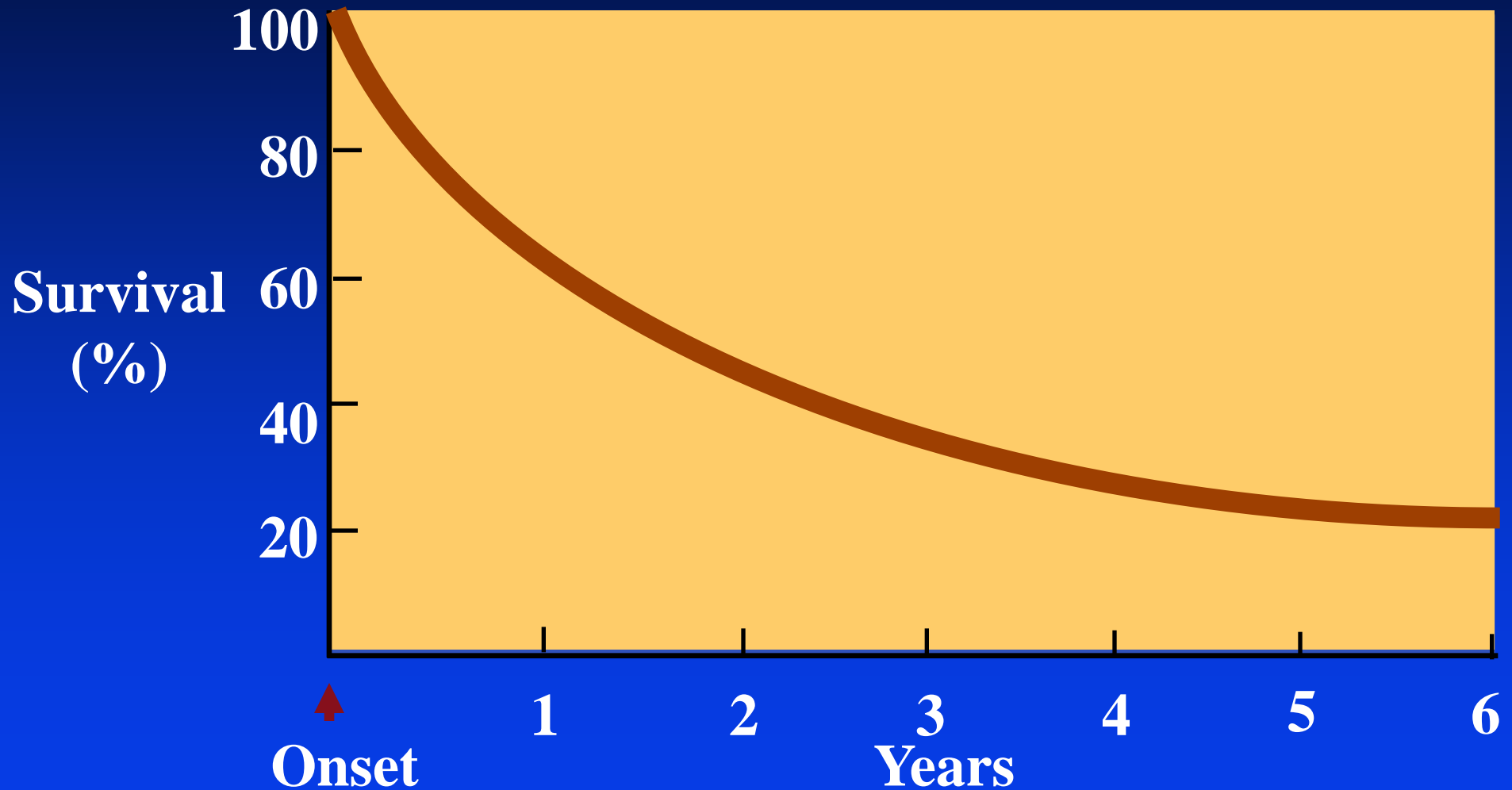
Complications of Cirrhosis

- **Ascites**
 - **Hepatorenal Syndrome**
 - **Spontaneous Bacterial Peritonitis (SBP)**
 - **Hepatic Hydrothorax**
- **Varices**
- **Hepatic Encephalopathy (HE)**
- **Hepatocellular Carcinoma (HCC)**

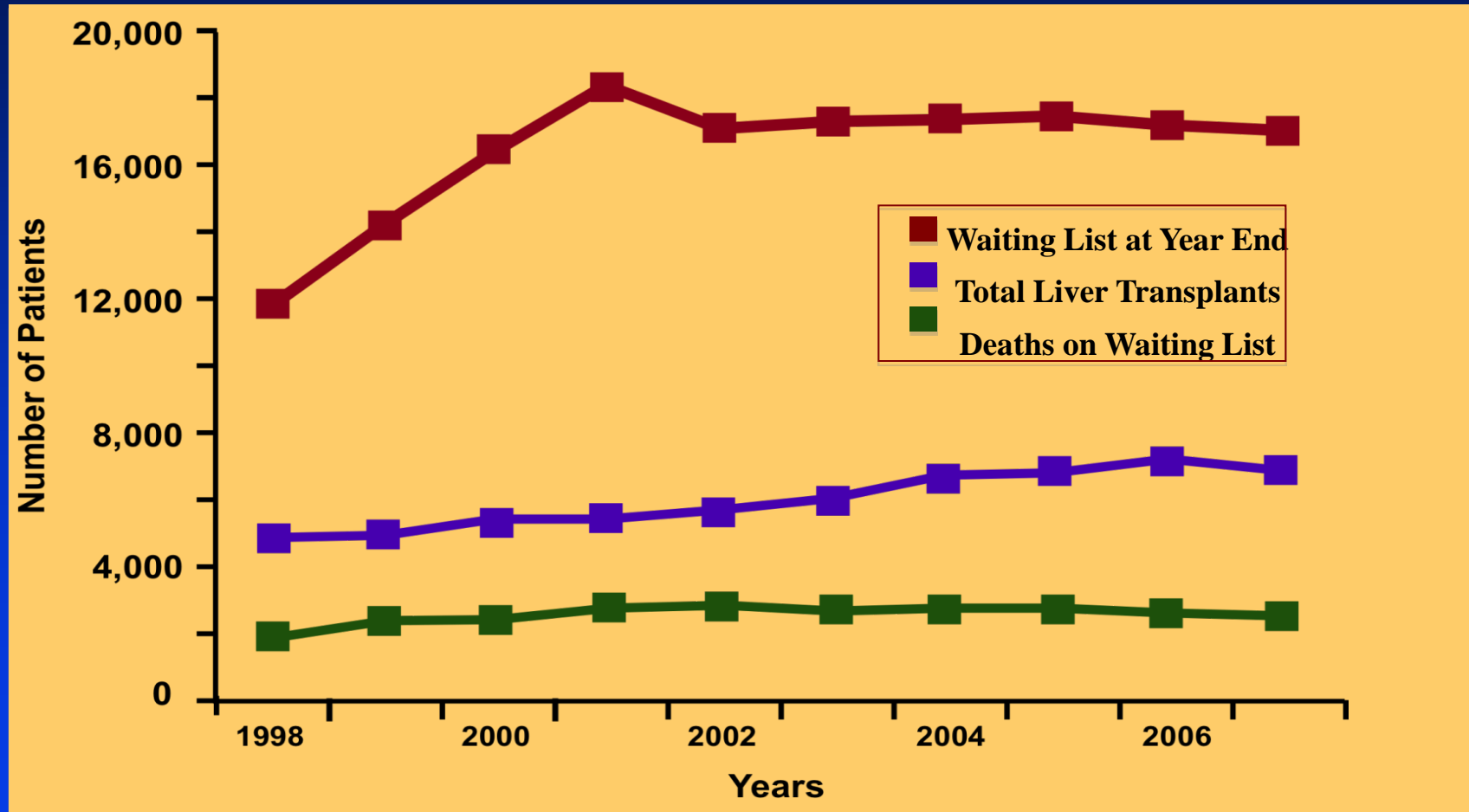
Ascites

- **Ascites is the most common of the three major complications of cirrhosis**
- **Approximately 50%-60% of compensated cirrhotics will develop ascites over 10 years of follow up**
- **Development of ascites is an important landmark in the natural history of cirrhosis indicating a 50% 2-year mortality**

Cirrhotic Ascites – Survival

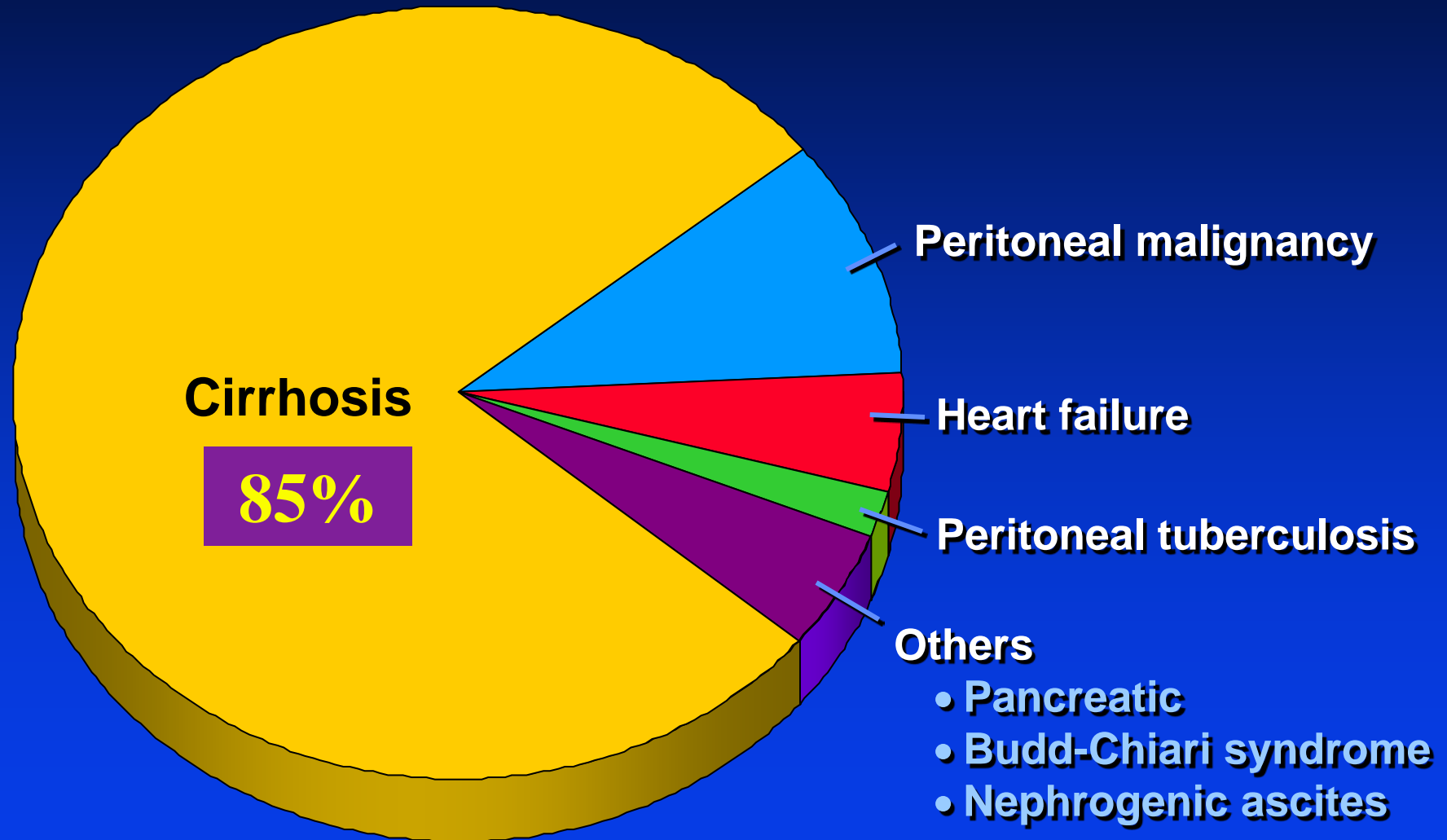


Wait List and Transplant Activity for Liver, 1998–2007

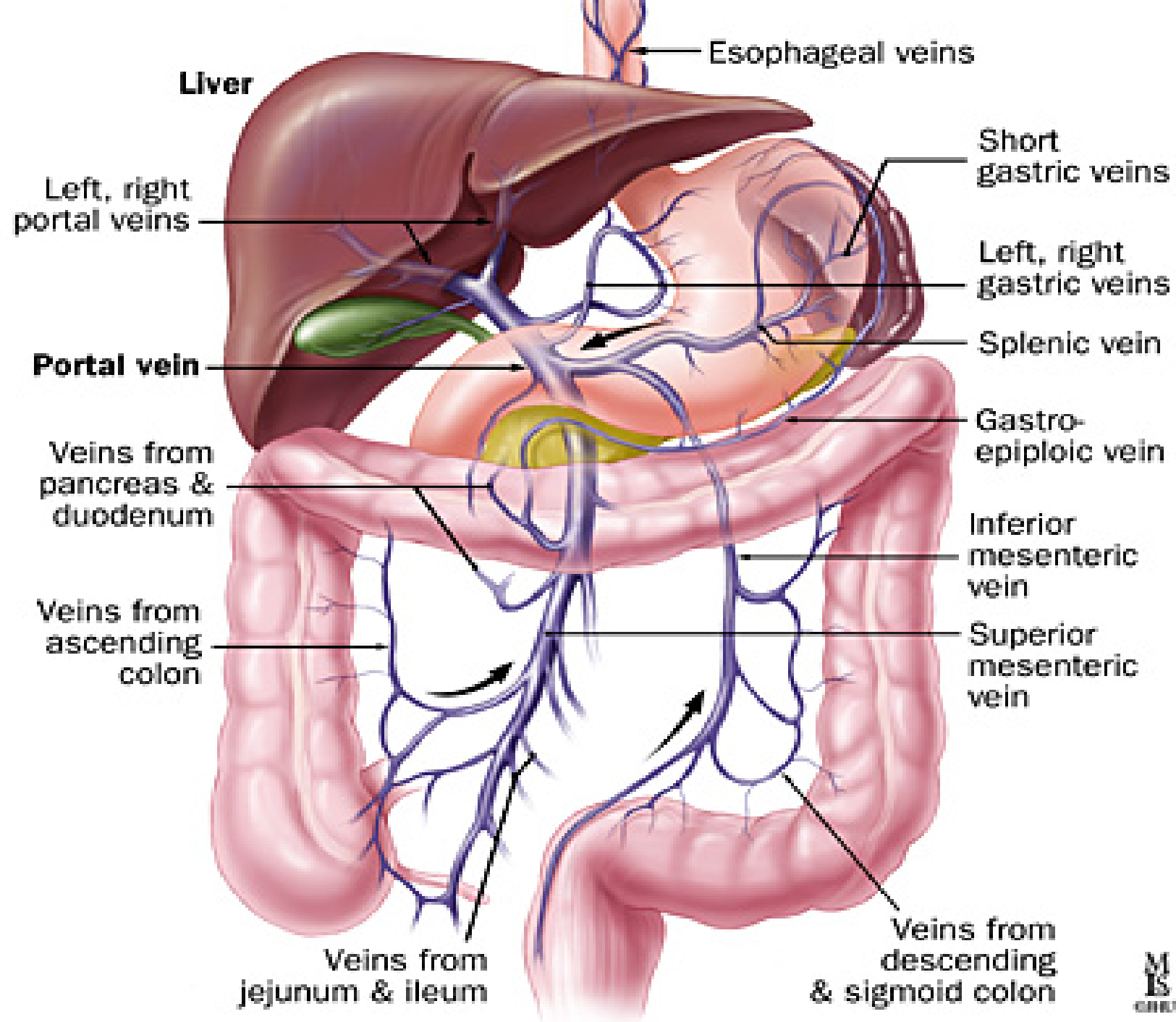


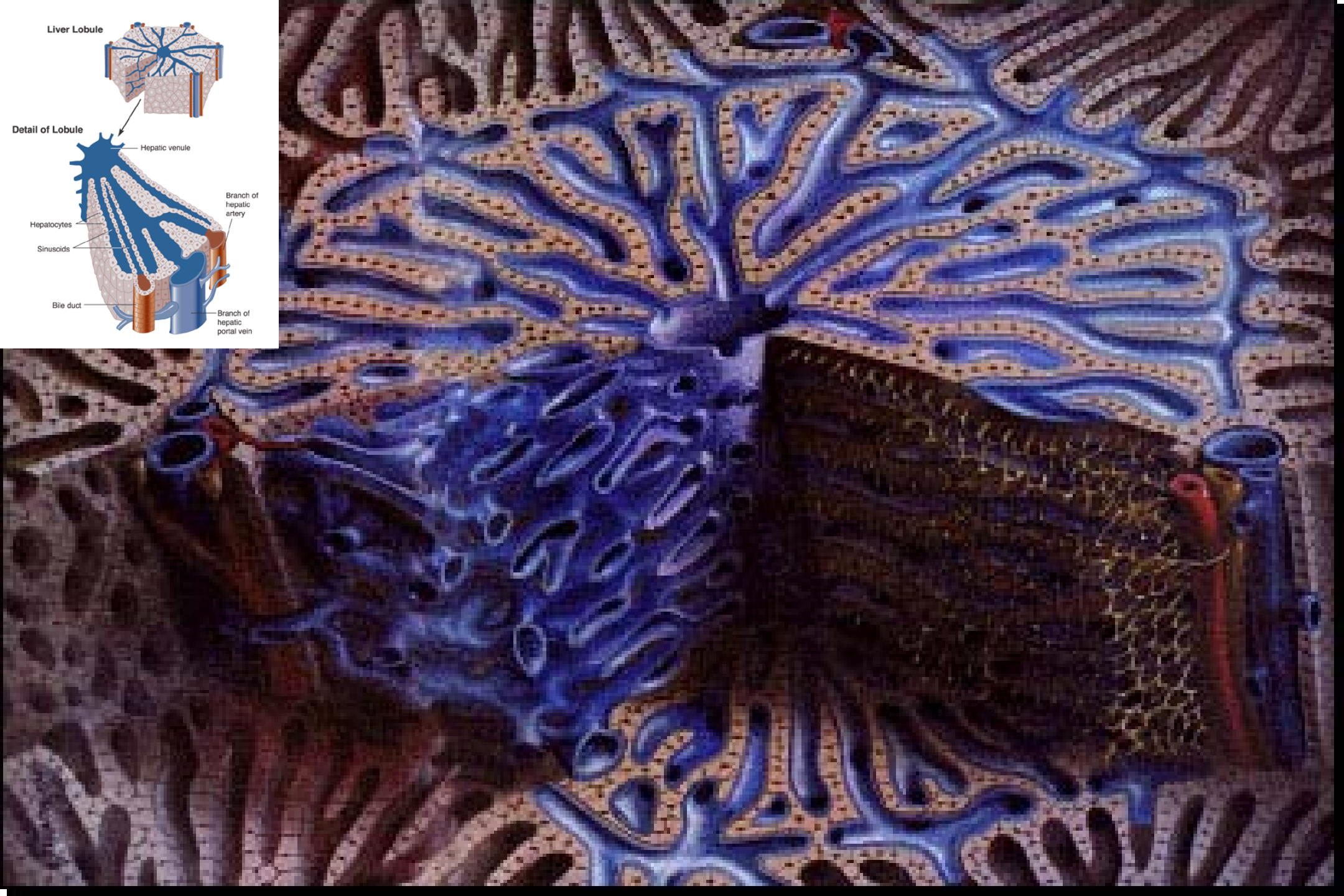
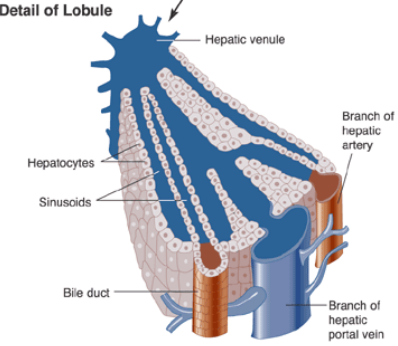
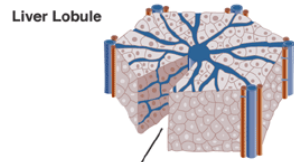


Cirrhosis is the Most Common Cause of Ascites



Normal Portal Anatomy

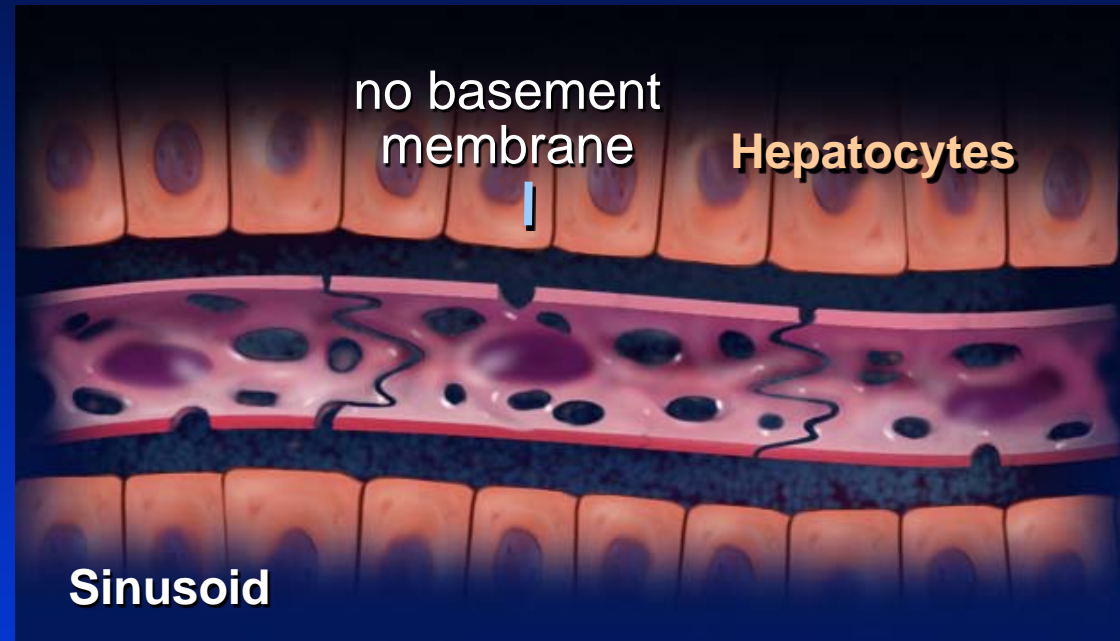
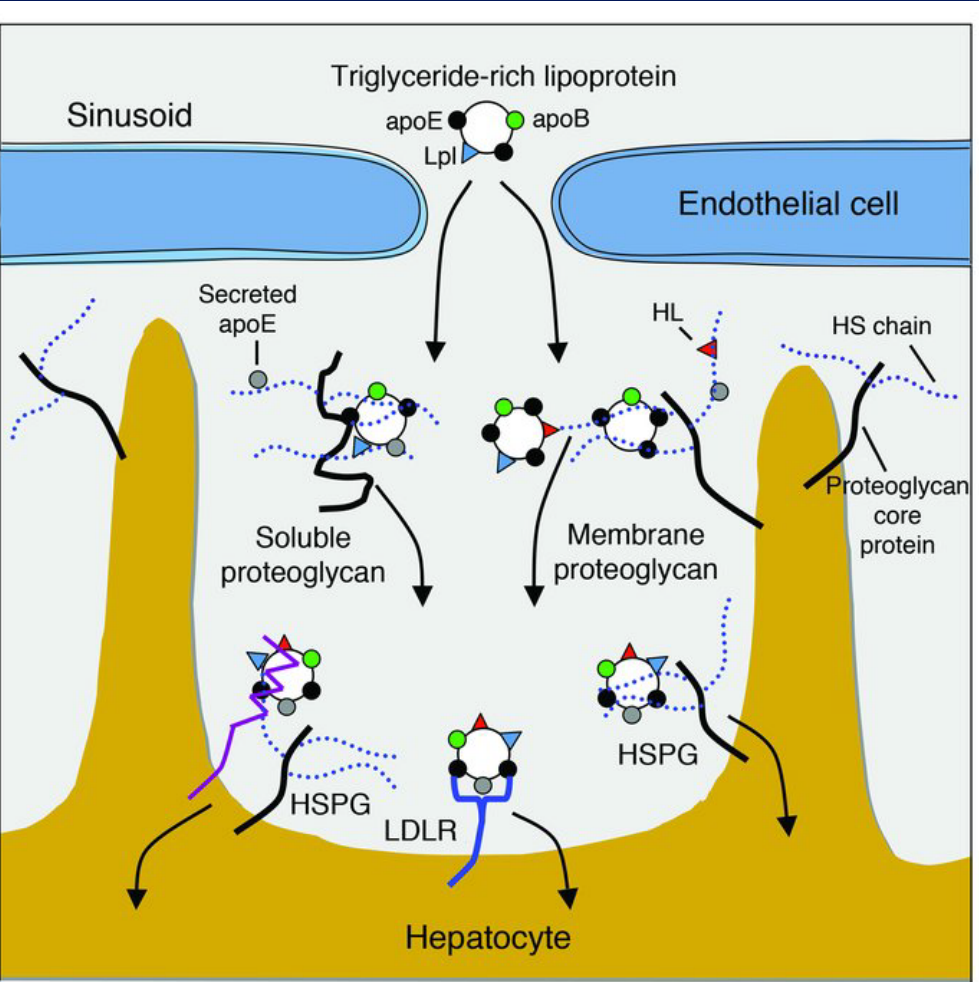




Hepatic Sinusoid

- Unlike other capillaries, normal hepatic sinusoids lack a basement membrane.
- The sinusoidal endothelial cells themselves contain large fenestrae (200-400 nm in diameter), allowing passage of large molecules with molecular weight up to 250,000.
- These two features make the normal hepatic sinusoid very permeable with movement of fluid depending mostly on hydrostatic pressure
- Normal portal sinusoid pressure is 3-4 mmHg

Hepatic Sinusoid

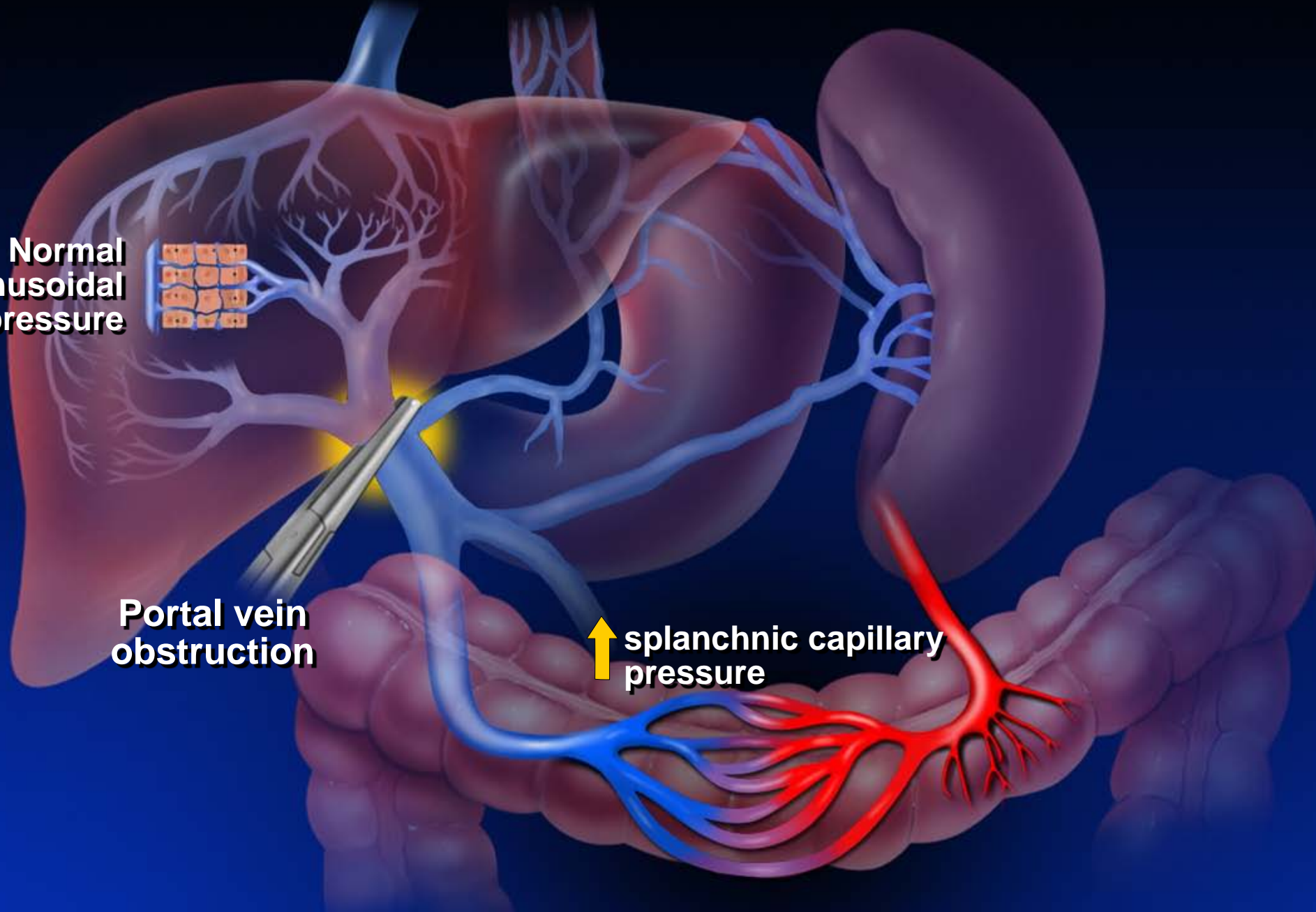


Portal Vein Obstruction Almost Never Leads to Ascites

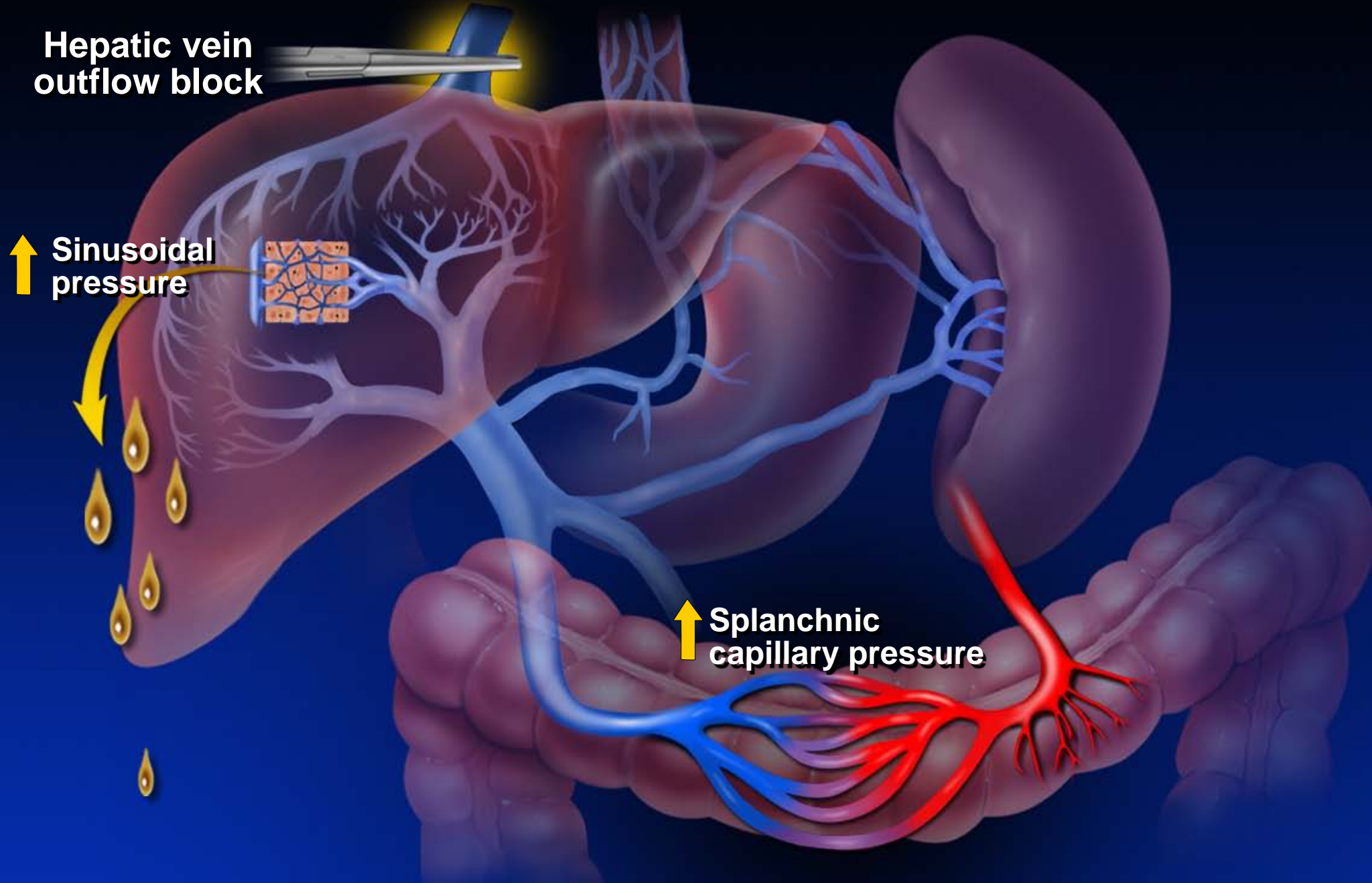
Normal
sinusoidal
pressure

Portal vein
obstruction

↑ splanchnic capillary
pressure

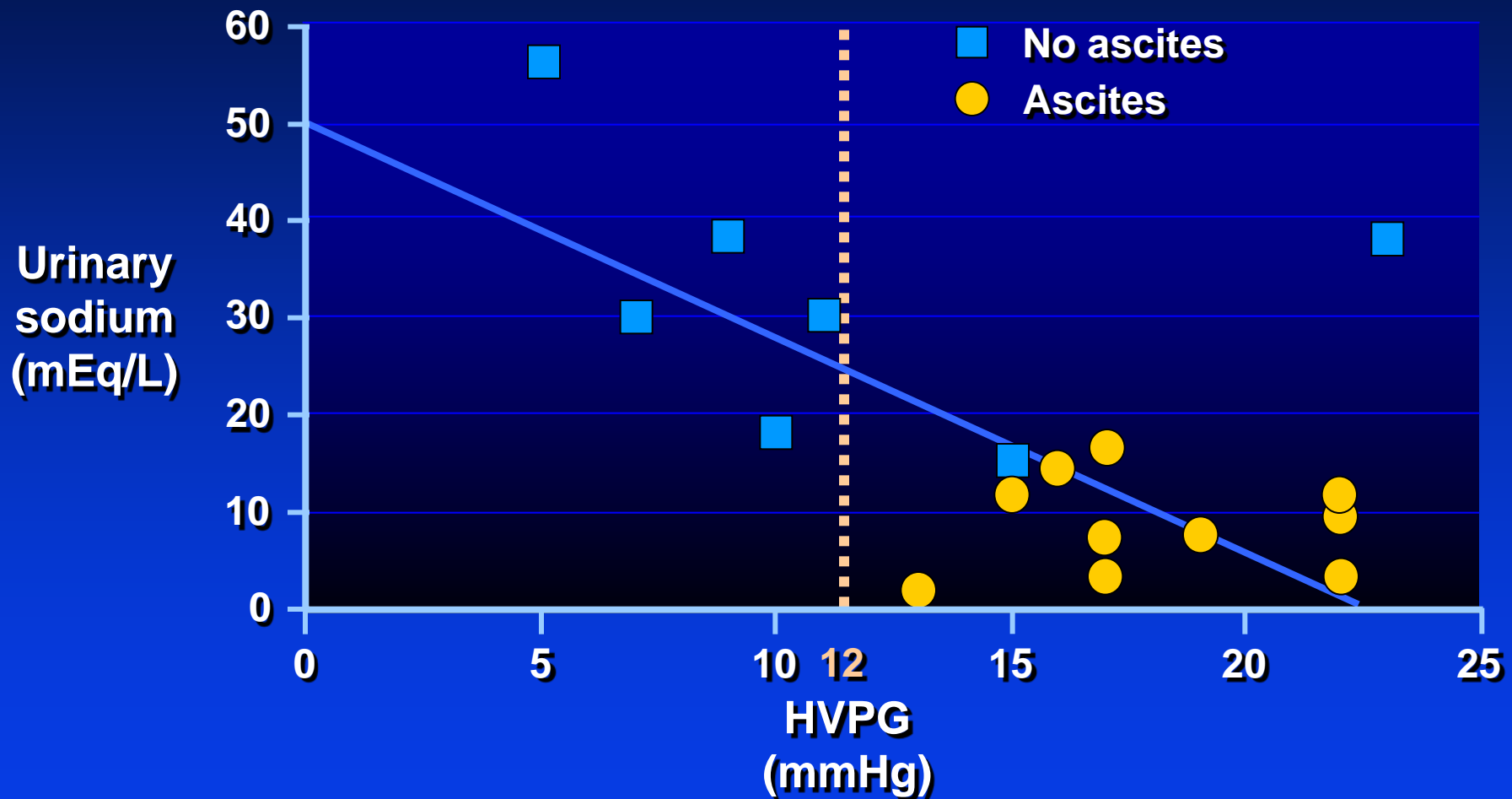


Hepatic Vein Obstruction Leads to Ascites Formation

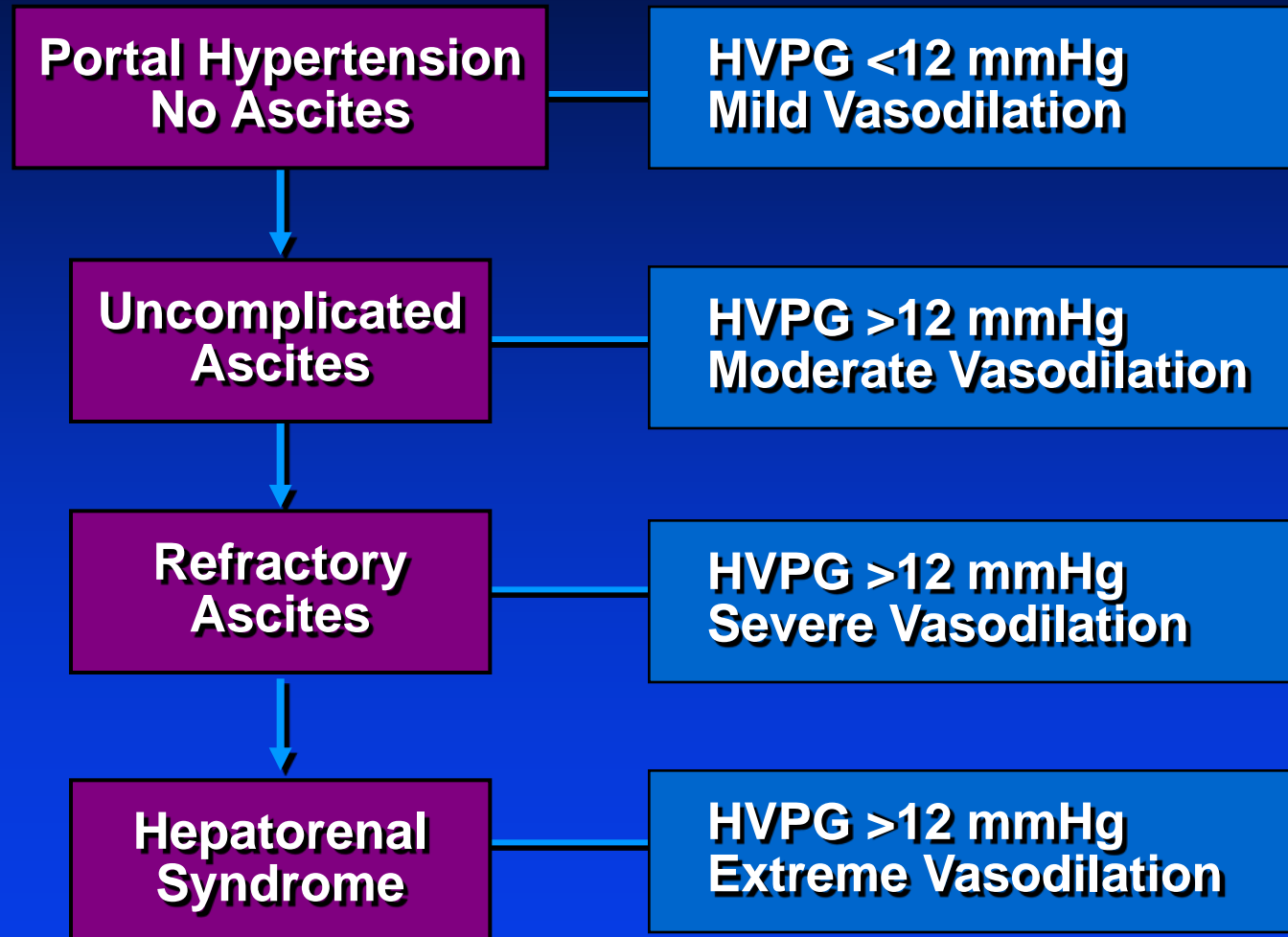




HVPG > 12 mmHg is Necessary for Ascites to Develop and is Associated with Low Sodium Excretion



Natural History of Ascites



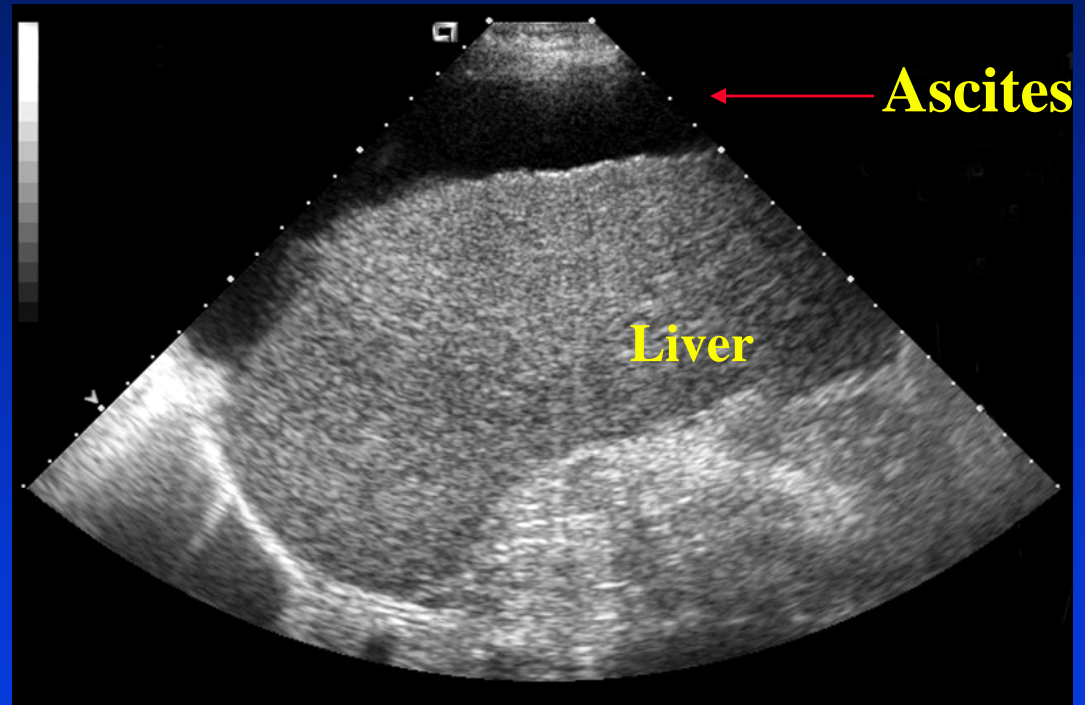
Ascites: Diagnosis

Ascites: Diagnosis

- **Physical examination is relatively insensitive in the diagnosis of moderate ascites**
 - **Sensitivity 50-94% Specificity 29-82%**
 - **Flank dullness is most specific sign**
 - **Approximately 1500 cc of fluid required for flank dullness**
 - **“Fluid wave” and “puddle sign” are not useful**
- **Almost all patients with cirrhosis severe enough to develop ascites have stigmata of cirrhosis on physical examination**

Ascites: Diagnosis

- Ultrasound is the gold standard detecting as little as 100 cc.
- Most cost-effective



Ascites: Paracentesis

- Abdominal paracentesis is the most rapid and cost-effective method of diagnosing the cause of ascites
- Paracentesis should be performed in all patients with new-onset ascites and recently-admitted inpatients with *established* ascites
 - 20 % prevalence of SBP/infection at time of admission
- Complications reported in only 1%, despite elevated INR in over 70%
 - Serious complications (hemoperitoneum or bowel entry) in <1/1000

Diagnostic Paracentesis

Indications

- New-onset ascites
- Admission to hospital
- Symptoms/signs of SBP
- Renal dysfunction
- Unexplained encephalopathy

Contraindications

- DIC



Ascites: Paracentesis

- **Coagulopathy should not preclude paracentesis unless there is clinically evident DIC**
- **There is no data-supported cutoff or coagulation parameters beyond which paracentesis should be avoided.**
- **Best location LLQ , 2 FB cephalad and 2Fb medial to ant. sup. Iliac crest.**



Ascites Fluid Analysis

Routine

- **Albumin**
- **Protein**
- **PMN cell count**
- **Cultures**

Optional

- **Glucose**
- **LDH**
- **Amylase**
- **Red blood cell count**
- **TB smear and culture**
- **Cytology**
- **Triglycerides**

Ascites: Analysis

- **For uncomplicated cirrhotic ascites, only three screening tests are initially indicated**
 - **Cell count**
 - **Albumin**
 - **Total protein**
- **If SBP suspected, bedside bacterial cultures optimal**
- **Serum-ascites albumin gradient (SAAG) is 97% accurate in diagnosis of portal hypertensive ascites**
- **Cytology and mycobacteria cultures should only be ordered for a high index of suspicion.**

Ascites Analysis

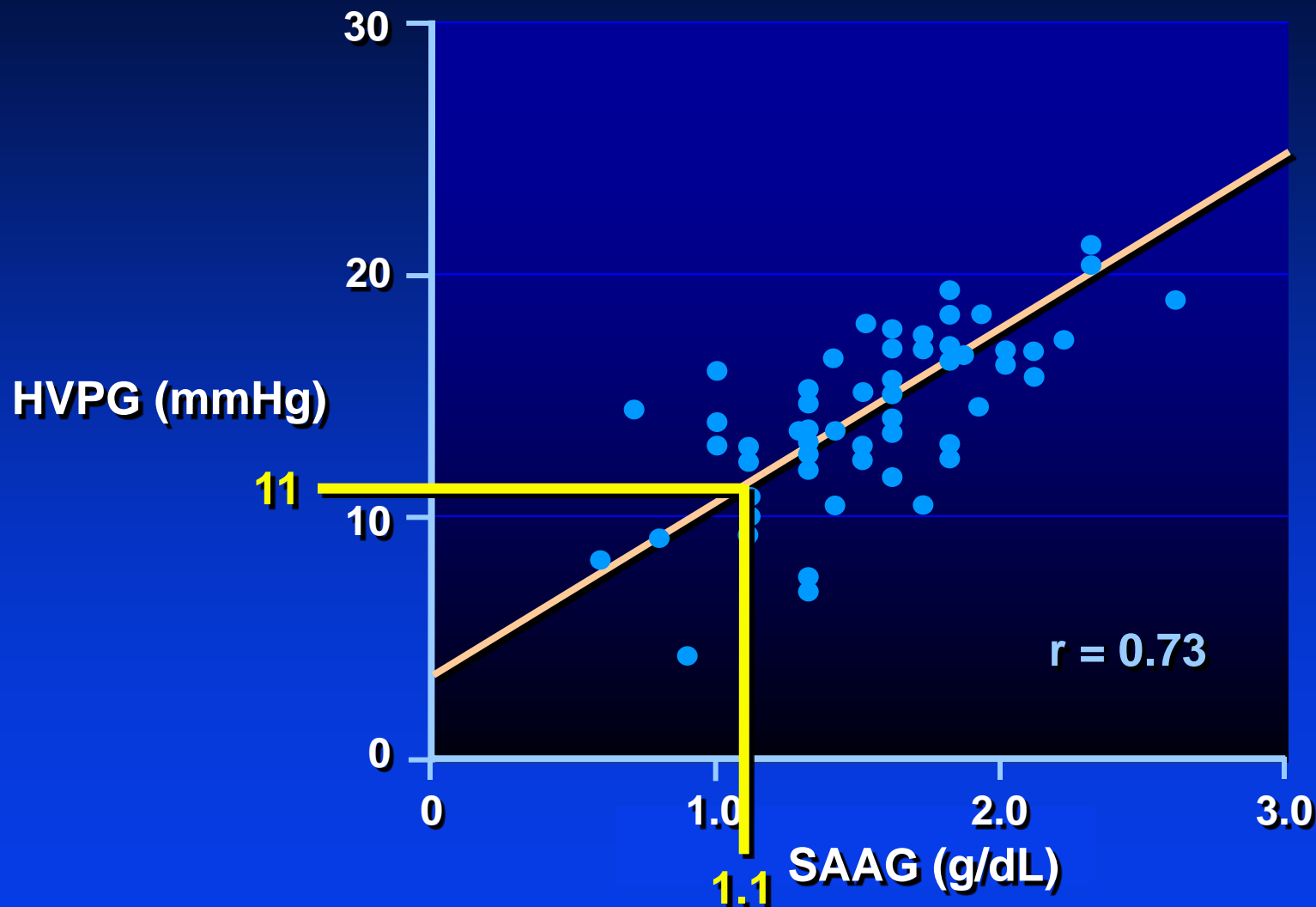
The three main causes of ascites, cirrhosis, right-sided heart failure and peritoneal pathology (malignancy or tuberculosis), can be easily distinguished by combining the results of both the SAAG and ascites total protein content

The Serum-Ascites Albumin Gradient (SAAG) Correlates With Sinusoidal Pressure

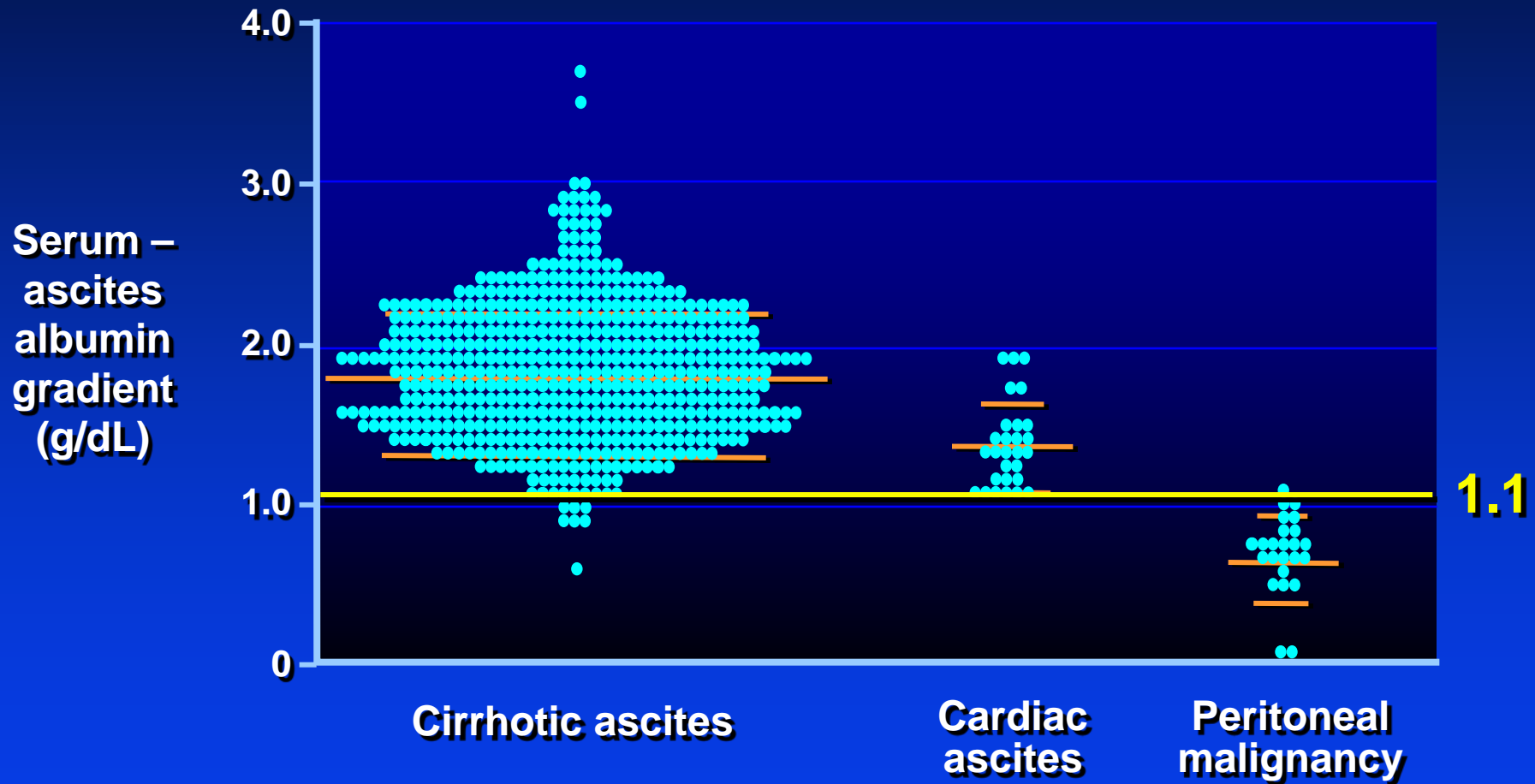
- **The serum-ascites albumin gradient (SAAG) is based on the fact that, per Starling forces, oncotic-hydrostatic balance is the major controlling force determining the protein concentration of fluid in the peritoneal cavity.**
- **The SAAG cutoff value that best distinguishes patients in whom ascites is secondary to liver disease and those with malignant neoplasm is a SAAG of 1.1 g/dL.**



The Serum-Ascites Albumin Gradient (SAAG) Correlates With Sinusoidal Pressure

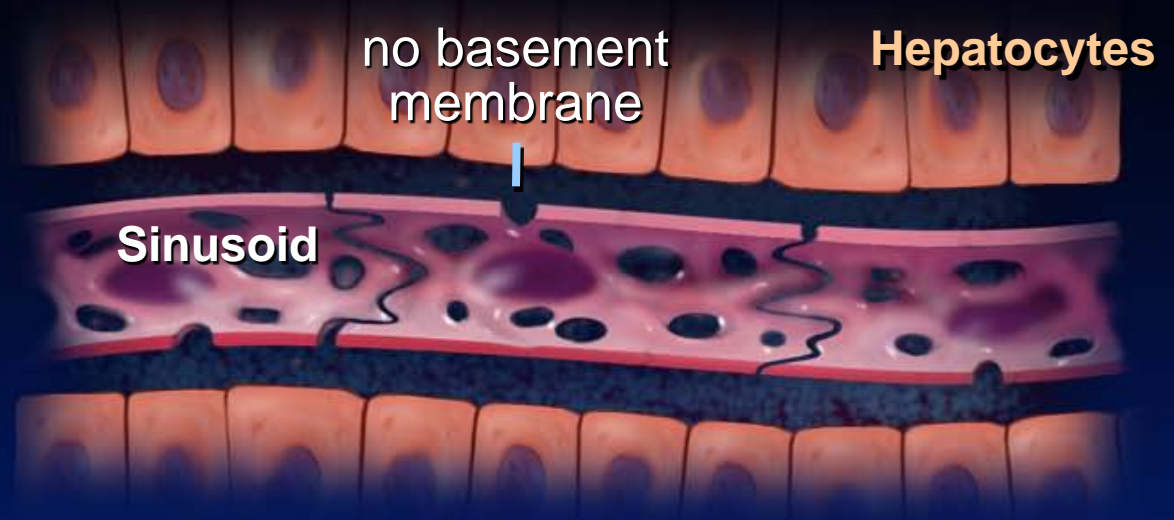


Serum-Ascites Albumin Gradient is High in Portal Hypertensive Causes of Ascites

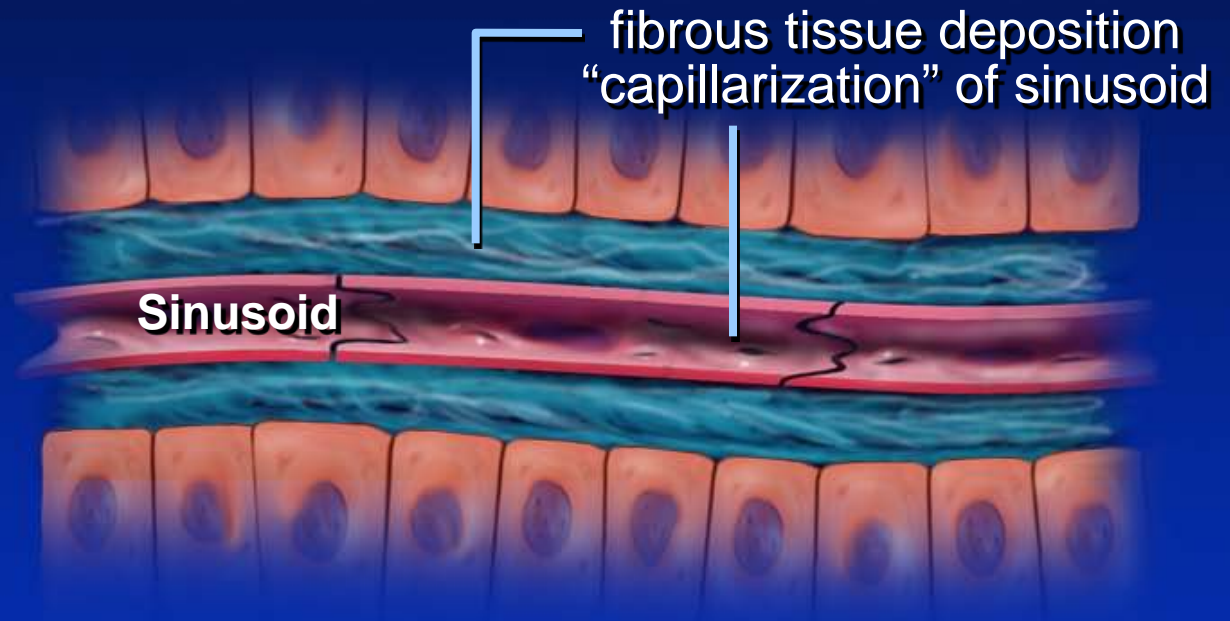


The Permeability of the Hepatic Sinusoid Varies in Health and Disease

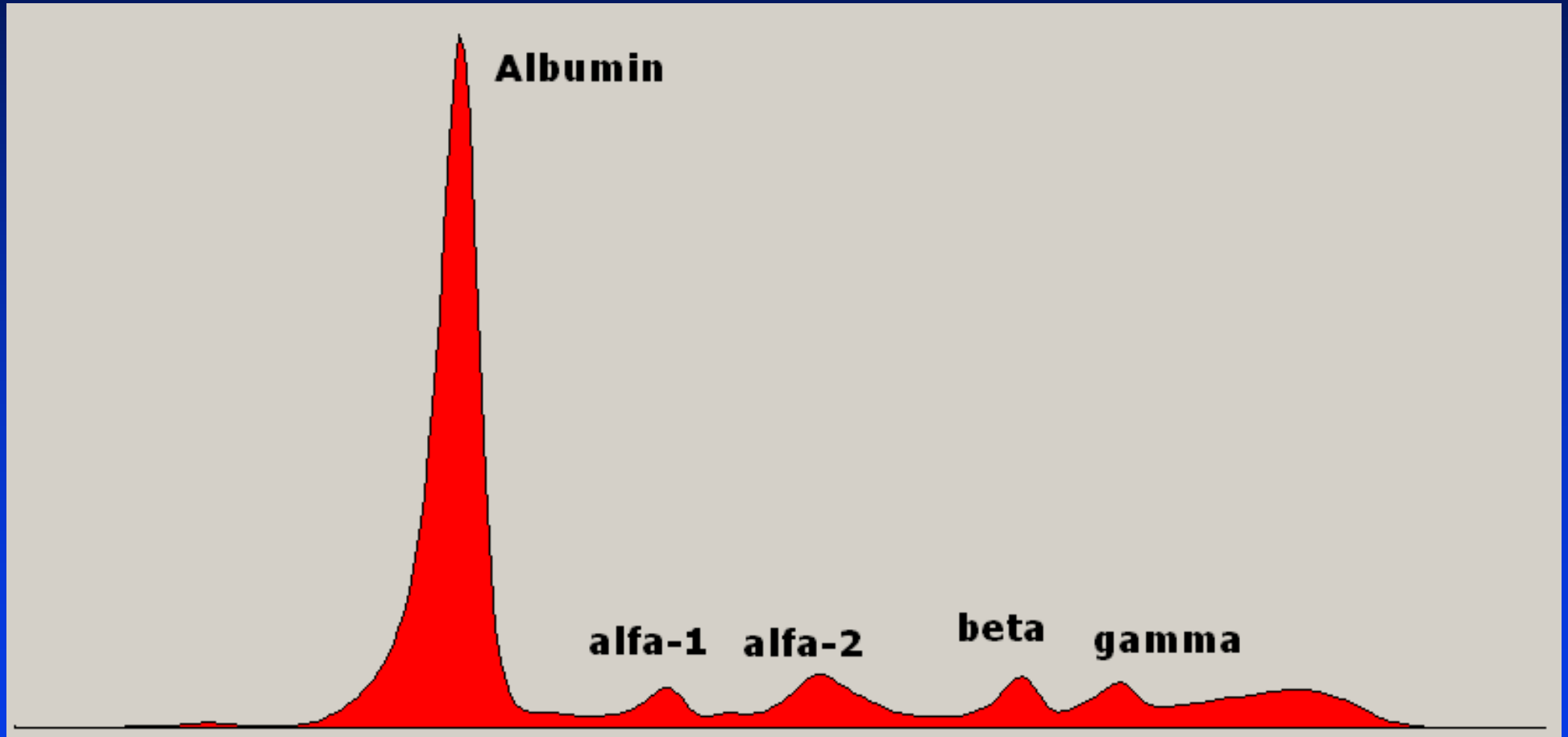
The normal sinusoid is “leaky”



In cirrhosis, the hepatic sinusoid is **less** leaky

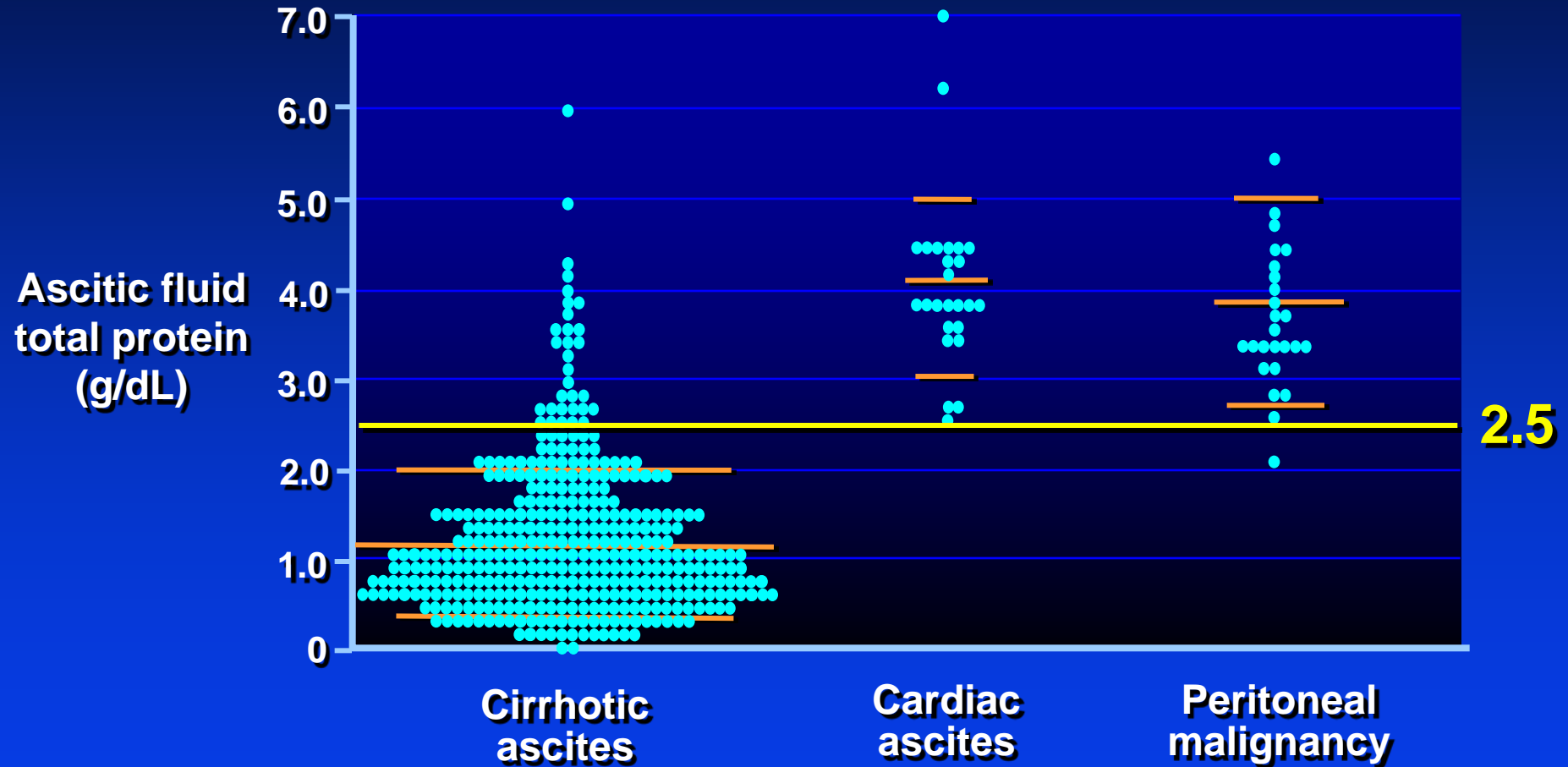


Larger Serum Proteins Less Likely to Traverse the Sinusoid Fibrosis

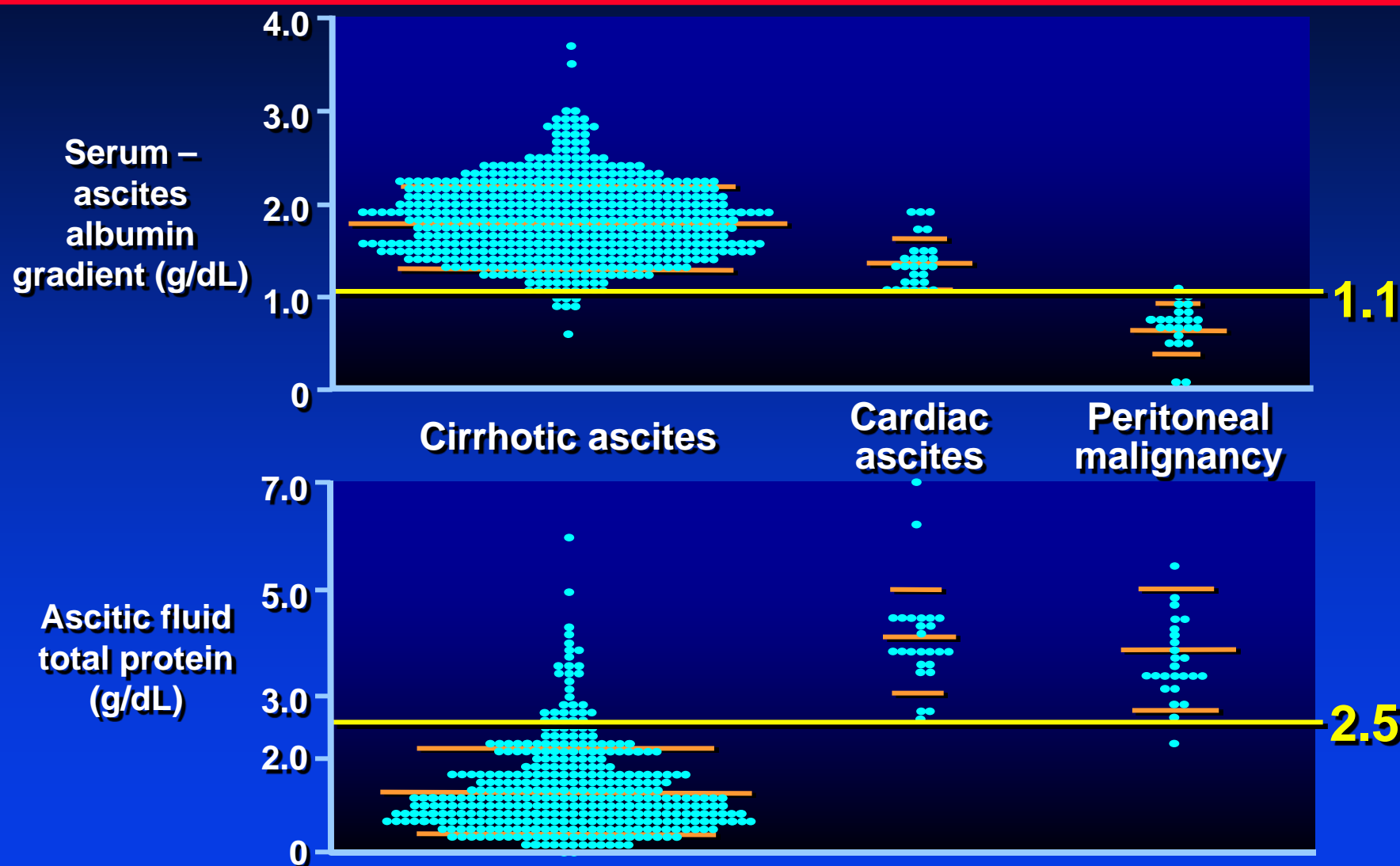




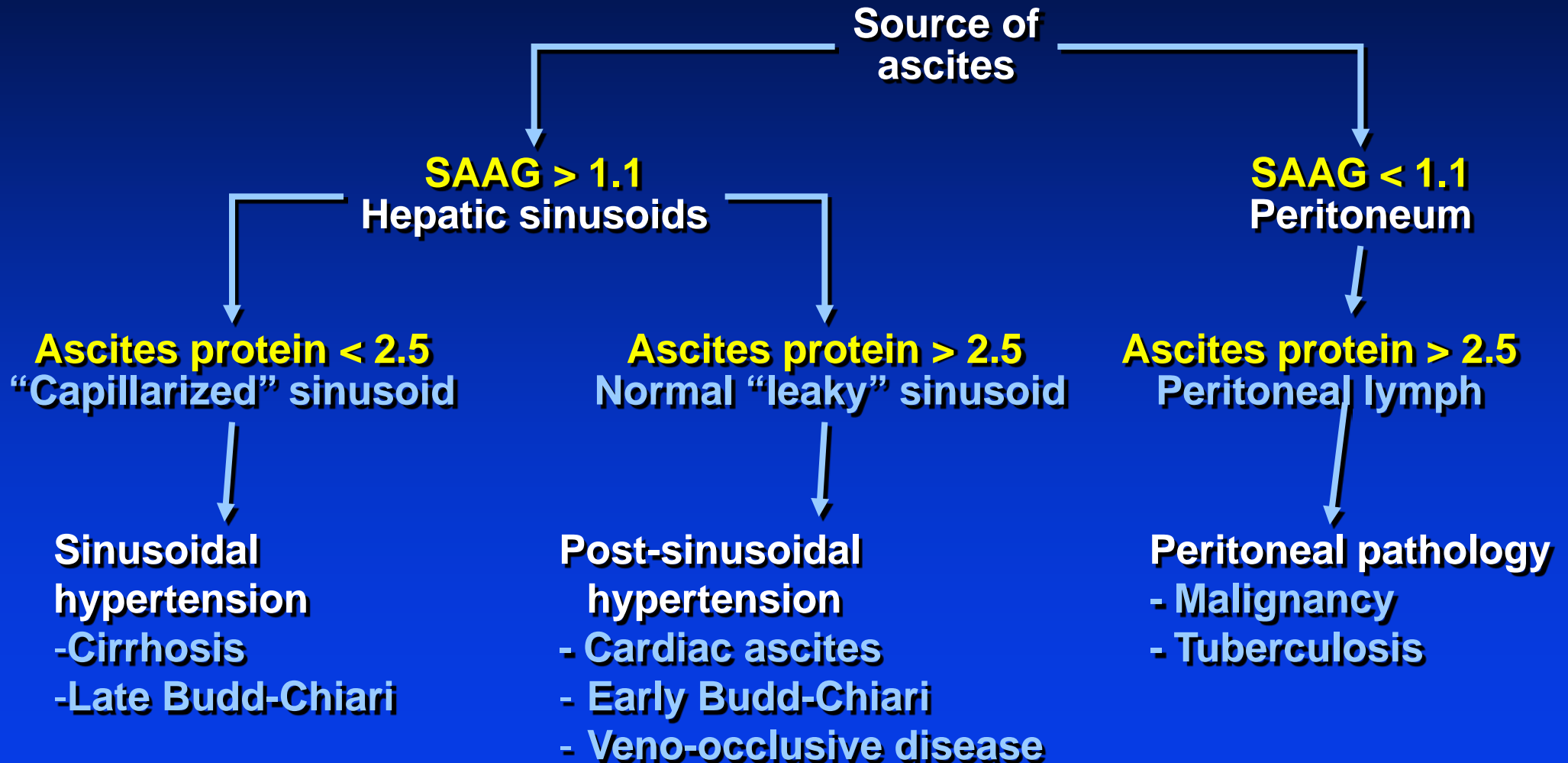
Ascites Total Protein is Elevated in Cardiac Ascites and Peritoneal Malignancy



Serum-Ascites Albumin Gradient and Ascites Protein Levels in the Most Common Causes of Ascites



Ascites Can Be Characterized by Serum-Ascites Albumin Gradient (SAAG) and Ascites Protein



Ascites: Additional Tests

- **Amylase**
 - **Pancreatic ascites**
- **Glucose: low when being consumed by bacteria or WBC**
 - **Carcinomatosis**
 - **Gut perforation**
- **Gram stain: limited sensitivity 7-10%**
 - **Required 10,000 bacteria/ml (medial bacterial concentration in SBP= 1/ml)**

Ascites: Additional Tests

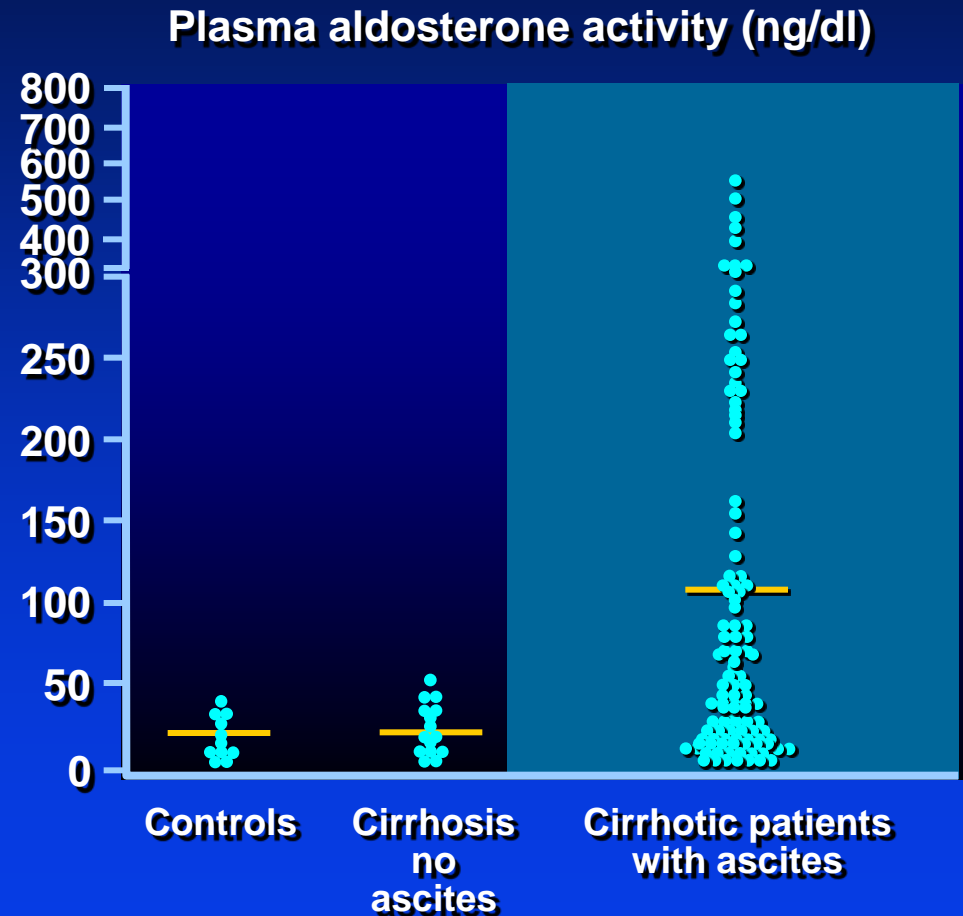
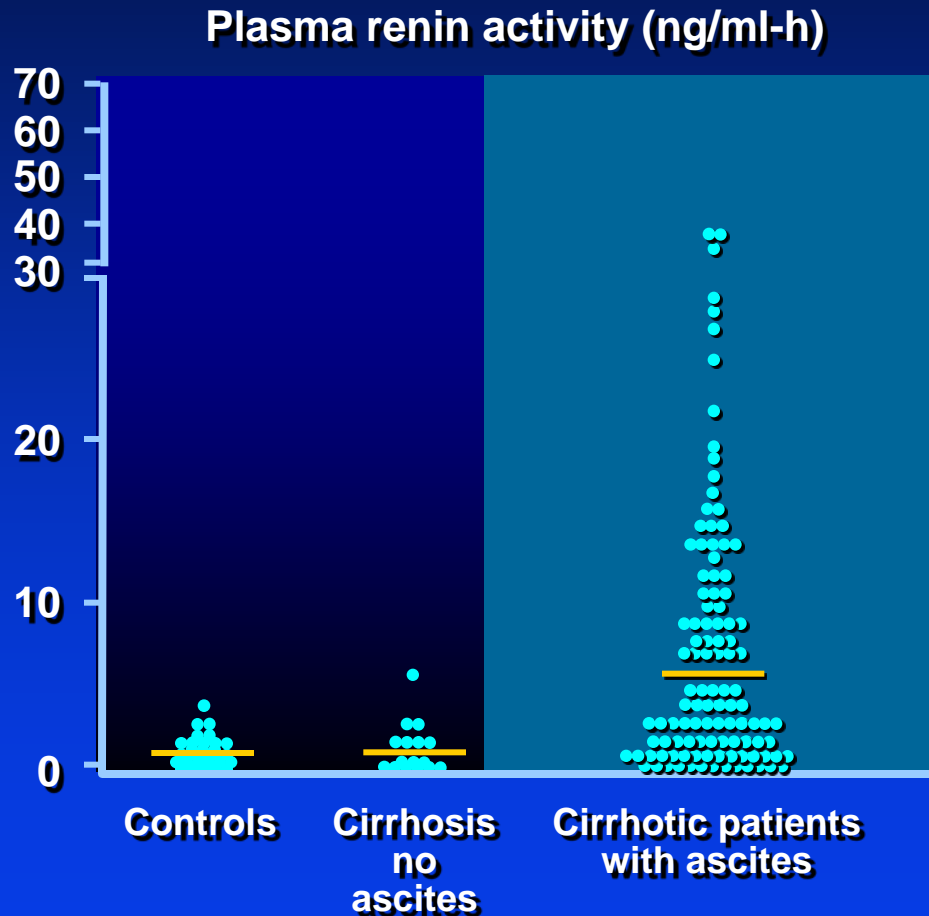
- **Cytology**
 - 100% sensitive for carcinomatosis
 - Only 2/3 of malignant ascites have carcinomatosis
 - Hepatocellular carcinoma
 - Massive liver metastasis
 - Chylous ascites due to lymphoma
- **Useless tests:**
 - pH
 - Lactate
 - CEA

Treatment

Ascites: Treatment

- **Successful treatment depends upon accurate diagnosis of the cause**
 - **Diuretics/sodium restriction ineffective in malignant, nephrogenic, and pancreatic ascites**
- **If possible, treat underlying cause of the decompensated cirrhosis**
 - **ETOH: abstinence**
 - **Autoimmune Hepatitis: steroids, AZA**
 - **Hepatitis B: antivirals**

Neurohumoral Systems are Activated in Cirrhotic Patients with Ascites



Ascites: Treatment

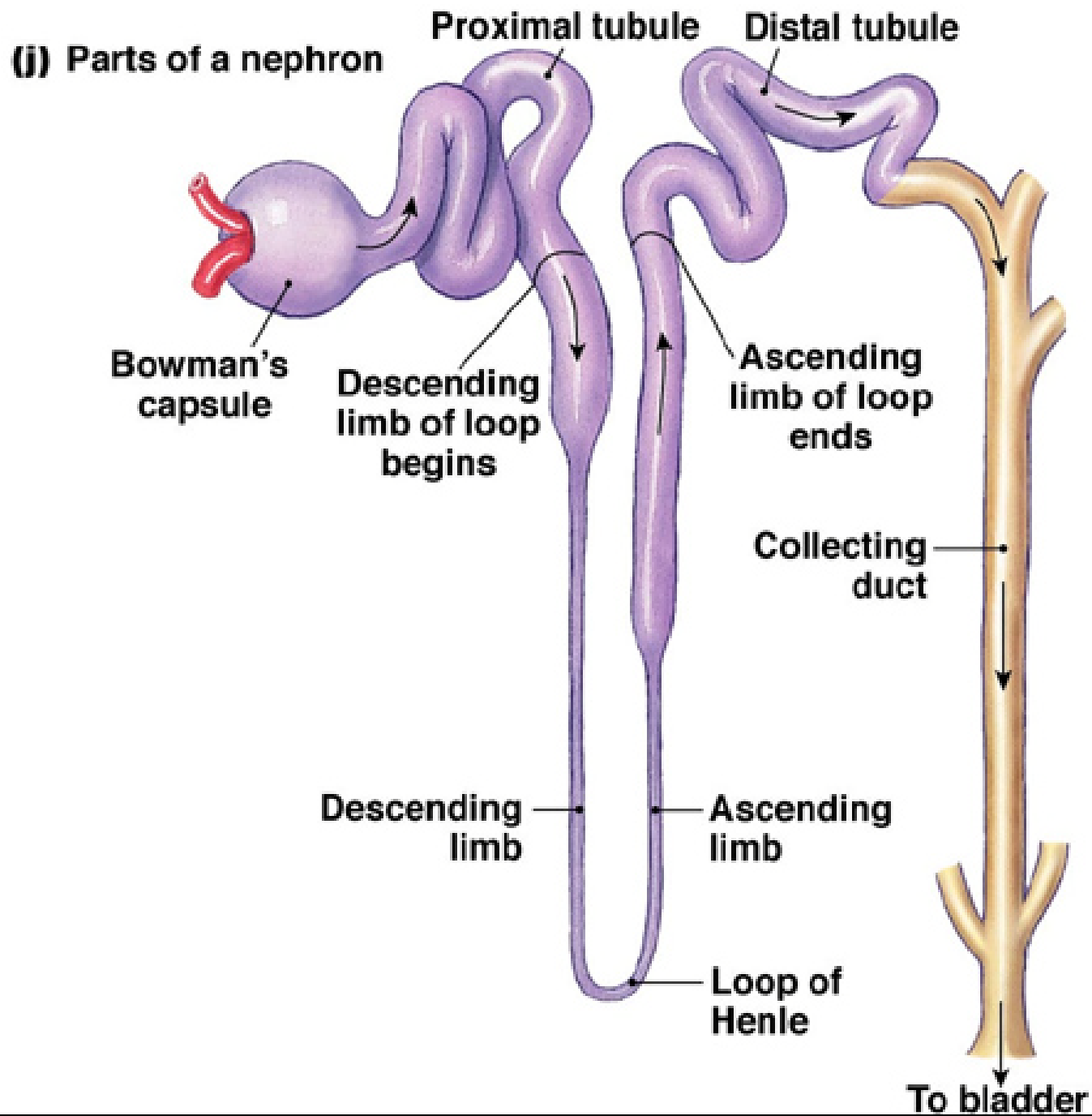
- **Goals:**
 - Minimize ascitic volume and peripheral edema
 - Avoid intravascular volume depletion
- **Benefits**
 - Patient comfort
 - Reduced risk of hernia formation
 - Possible reduction in SBP due to increased concentration of ascitic fluid opsonins
 - Improved nutrition

Treatment: Create Negative Sodium Balance

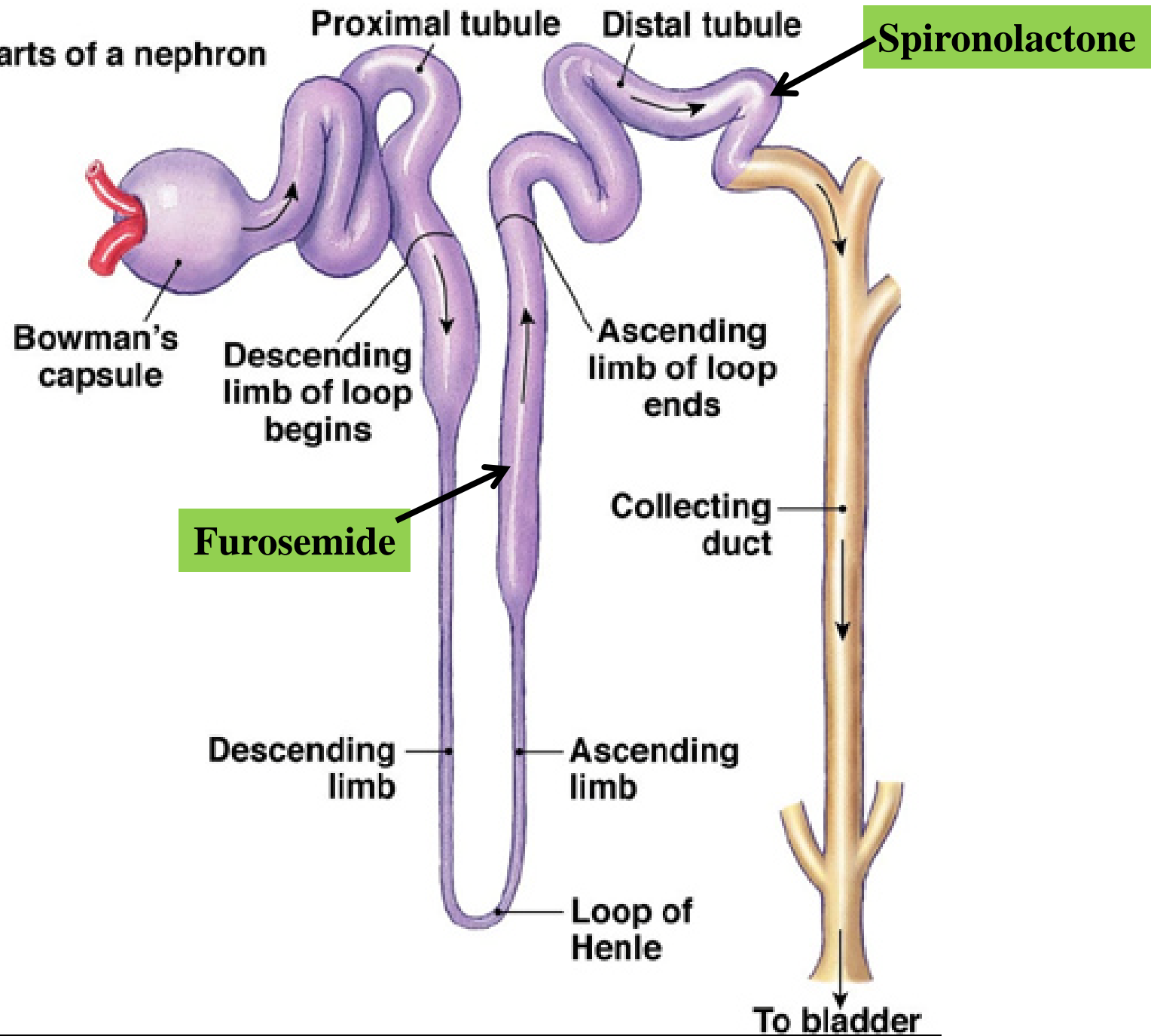
- The typical patient with ascites excretes < 20 meq sodium/day
- The typical North American diet contains 200-300 meq sodium/day
- No-added salt diet = 100-150 meq sodium
- A diet containing 88 meq sodium/day is the best compromise between salt restriction and acceptable palatability

Treatment: Create Negative Sodium Balance

- Dietary sodium restriction is essential to effective management of ascites
- 140 meq sodium = 1 liter of retained fluid
- Fluid loss follows sodium loss, so fluid restriction is rarely necessary
- Hyponatremia is common with ascites and does not require treatment if the Na > 130 meq/l
- The vast majority of patients require diuretics



(j) Parts of a nephron



Treatment: Diuretics

- The most successful regiment is a combination of a single morning oral dose of
 - spironolactone 100mg
 - furosemide 40 mg
- Maximizes compliance and minimizes nocturia
- The absorption of spironolactone is improved if given with food

Treatment: Diuretics

- Both proximal and distal acting diuretics needed to achieve diuresis
- Half life 4-6 hours
- Furosemide is filtered in the glomerulus and blocks sodium reabsorption on the luminal side
- A concentration-dependent threshold effect is observed

Rational Use of Furosemide

Furosemide half-life 4-6 hours

**Luminal
Concentration
Furosemide**

Diuretic Threshold

**Furosemide
40 mg**

8 AM

8 PM



Rational Use of Furosemide

Furosemide half-life 4-6 hours

**Luminal
Concentration
Furosemide**

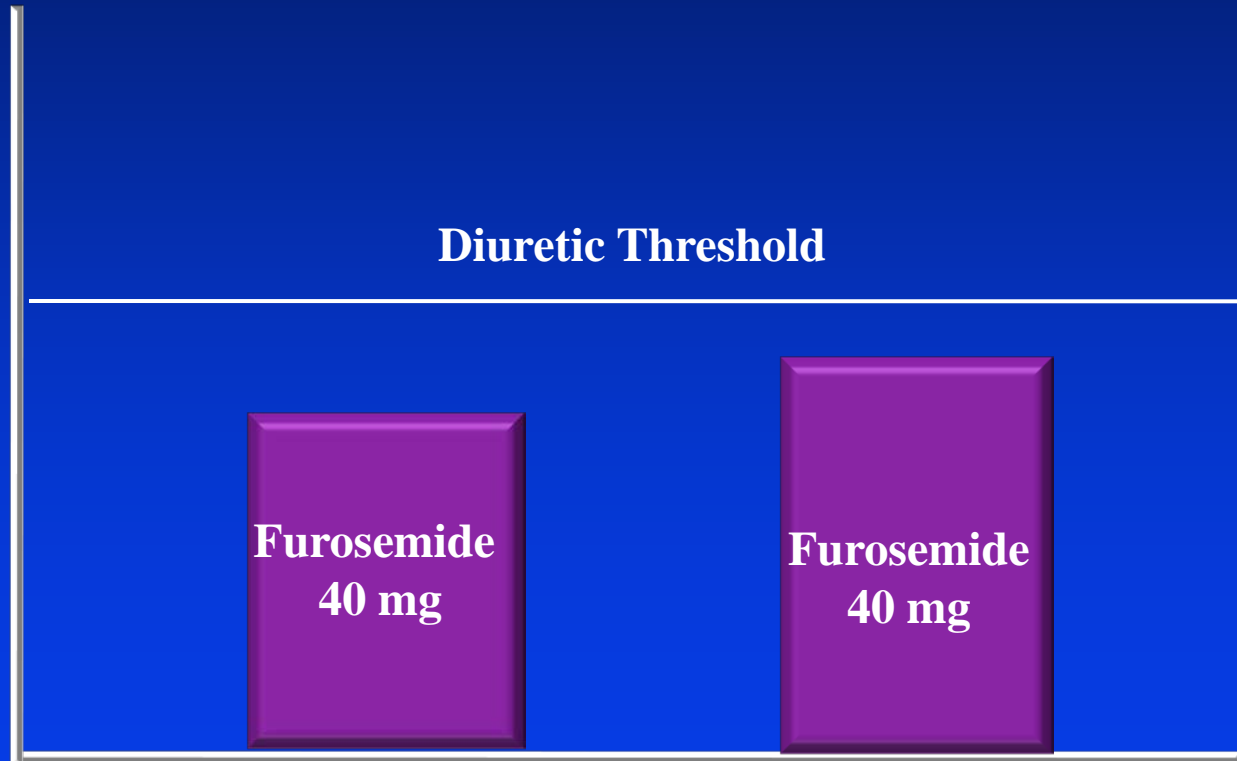
Diuretic Threshold

**Furosemide
40 mg**

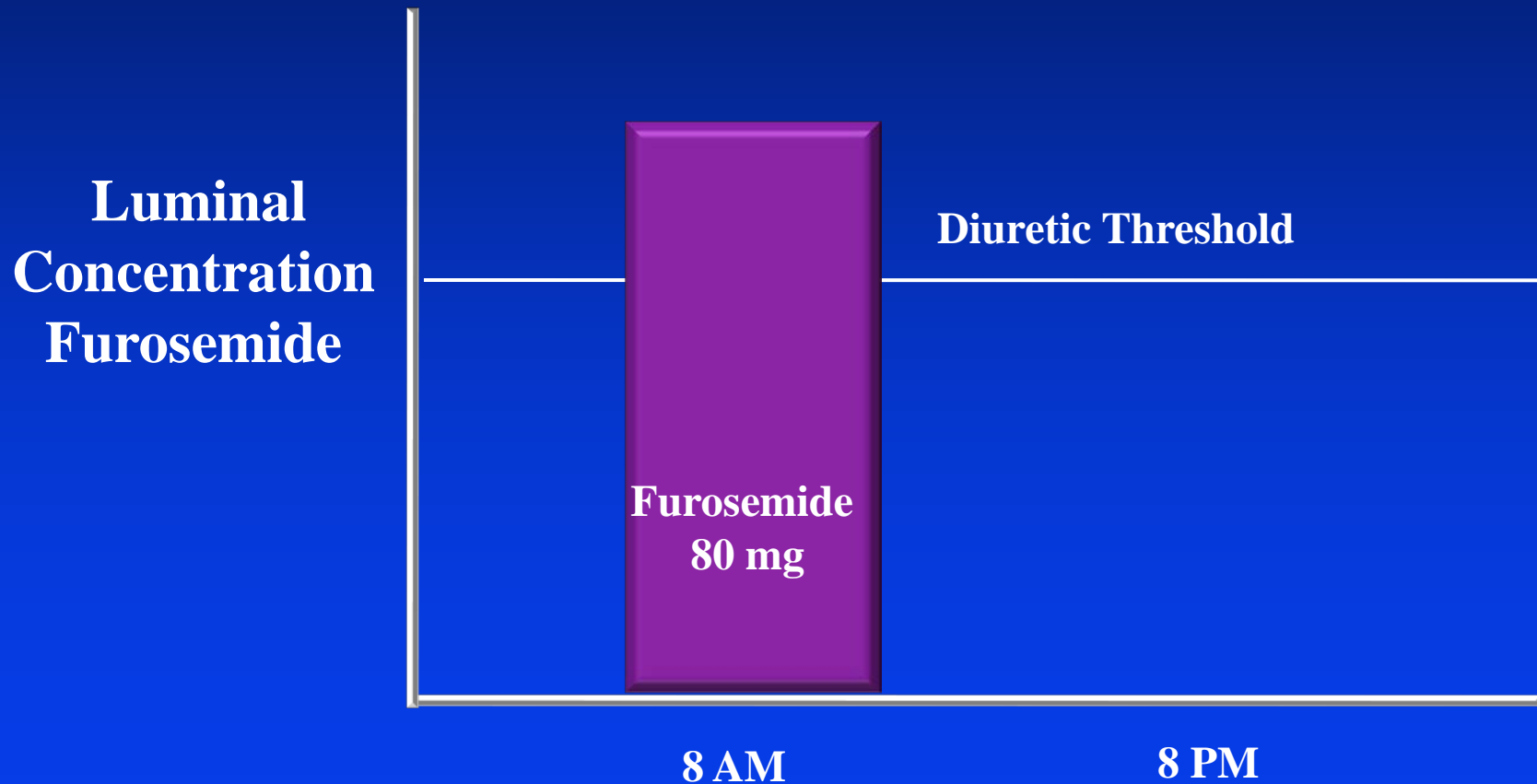
**Furosemide
40 mg**

8 AM

8 PM



Rational Use of Furosemide



Treatment: Diuretics

- The diuretic effect of spironolactone is seen within 48 hours and peaks at 2 weeks
- Dose should be adjusted no more often than once every 5-7 days
- Doses can be doubled in the absence of diuresis to a maximum of spironolactone 400 and furosemide 160 mg/day
- The spironolactone/furosemide ratio of 100/40 should be maintained to maintain normokalemia

Urine Electrolytes and Treatment Decisions

Untreated Urine Lytes
NA < 10 mEq/K > 40 mEq



2 gram (88 mEq) sodium diet
Furosemide 40 mg + Spironolactone 100 mg

Inadequate Diuresis



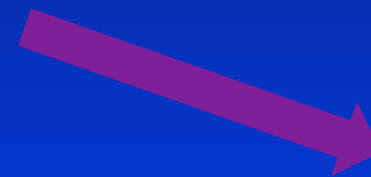
NA = 20 mEq
K = 20 mEq

Increase
Furosemide



NA = 40 mEq
K = 60 mEq

Increase
Spironolactone



NA = 100 mEq
K = 20 mEq

Discuss Dietary
Compliance

Treatment: Diuretics

- **Two major concerns**
 - **Avoid overly rapid diuresis: pre-renal azotemia**
 - **Progressive electrolyte imbalance**
- **Rate of safe diuresis is a function of presence or absence of peripheral edema**
 - **Peripheral edema = rate unlimited**
 - **The maximum rate of mobilization of ascites via peritoneal capillaries is 500-700 cc/day**
 - **Weight loss should not exceed 0.5 kg/day**

Medical Management of Ascites

- Combination of proximal and distal acting diuretics essential
- Patient education on critical function of sodium restriction
- Use urine electrolytes to guide treatment decisions
- Avoid NSAIDs
- Rate of diuresis with edema = 1 kg/day
- Rate of diuresis without edema = 0.5 kg/day

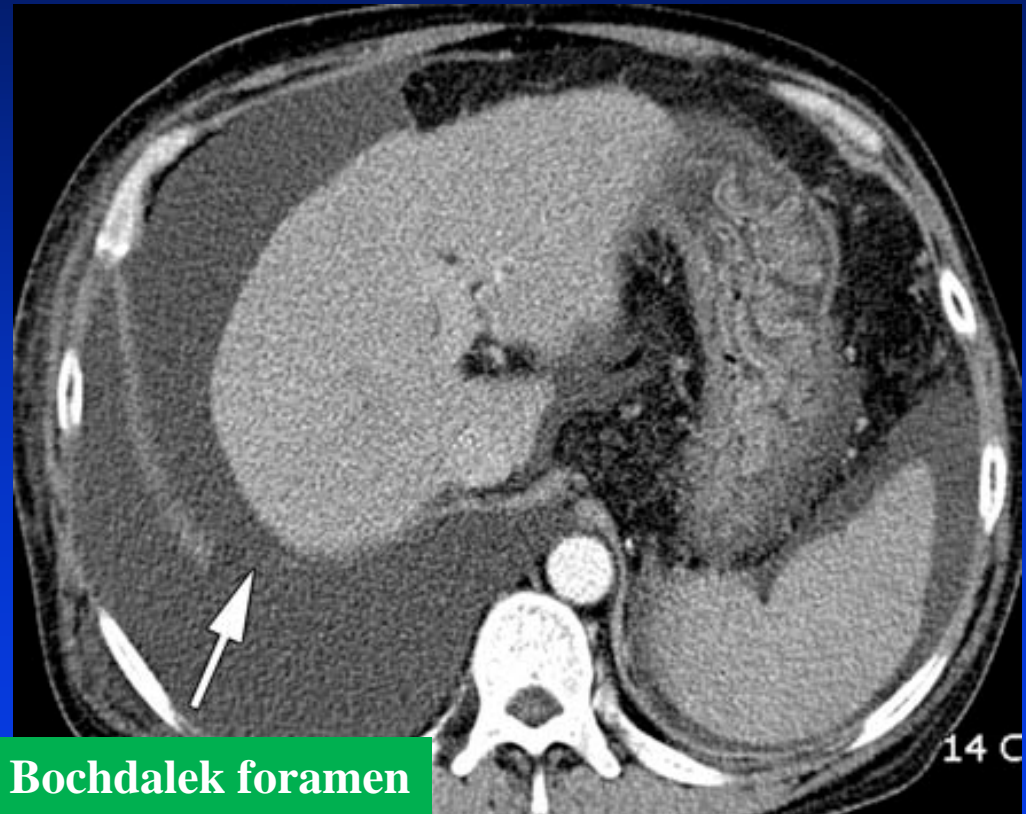
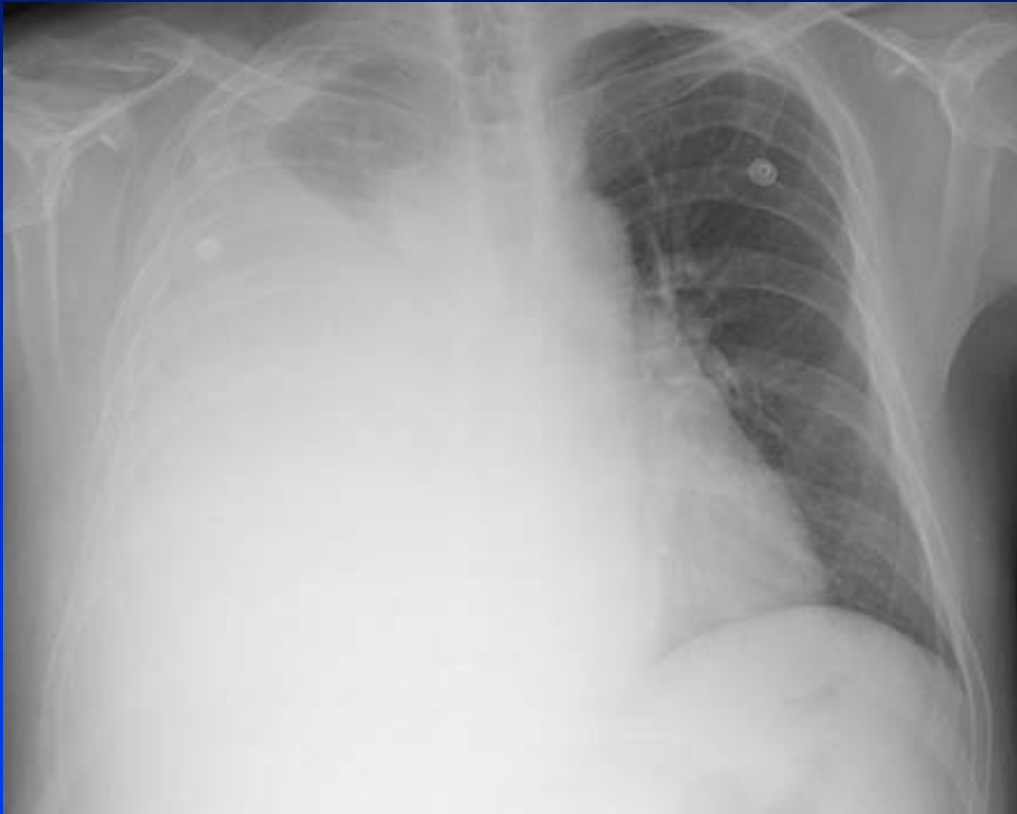
Up to 20% of Patients with Cirrhotic Ascites Fail Medical Management

- **Incorrect use of diuretics**
- **Dietary sodium abuse**
- **Hepatic Hydrothorax**
- **Hyponatremia**
- **SBP**
- **True refractory ascites**

Hepatic Hydrothorax

- **Most commonly on the right**
- **Reflects movement of ascites into the pleural space via defects in diaphragm**
- **May be seen in the absence of clinical abdominal ascites**
- **Fluid characteristics identical to ascites**

Hepatic Hydrothorax



Bochdalek foramen

Hepatic Hydrothorax: Treatment

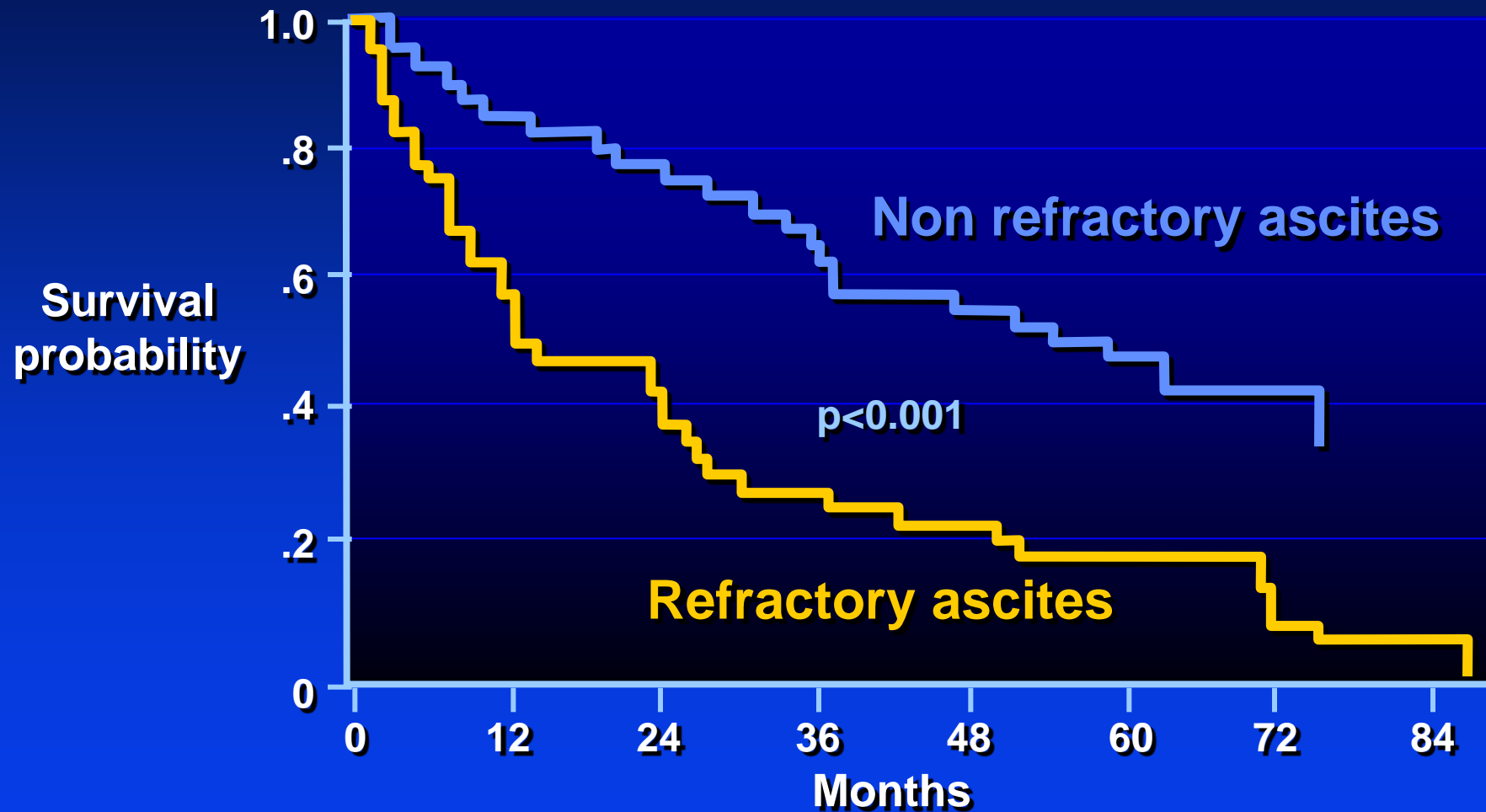
- **Do not place a chest tube or attempt pleurodesis**
- **Most cases respond to an increase in diuretics**
- **Refractory cases may require TIPS**

Refractory Ascites

Refractory Ascites

- Refractory ascites is one of the most dreaded complications of cirrhosis
- Increases the risk of further complications
 - SBP
 - Hepatorenal Syndrome
- Markedly compromises quality of life
- Associated with 50% 12 month mortality
- Usually an indication for transplant evaluation

Patients with Refractory Ascites Have A Worse Survival than Patients with Diuretic-Responsive Ascites



Definition and Types of Refractory Ascites

Occurs in ~10% of cirrhotic patients

- **Diuretic-intractable ascites 80%**

Therapeutic doses of diuretics cannot be achieved because of diuretic-induced complications

- **Diuretic-resistant ascites 20%**

No response to maximal diuretic therapy (400 mg spironolactone + 160 mg furosemide/day)

Refractory Ascites: Requisites

DEFINITION AND TYPES OF REFRACTORY ASCITES

- Lack of ascites mobilization on maximal tolerated diuretic dose for at least one week with a salt-restricted diet (<88meq sodium) and/or
- Diuretic-induced complication:
 - Cr > 2.0.
 - Hepatic encephalopathy
 - Progressive electrolyte imbalance
 - Hyponatremia,
 - Hypo- or hyperkalemia
- No NSAIDS

Refractory Ascites: Evaluation

- **Lack of compliance with sodium restriction is a common cause for apparent treatment failure**
- **24 hour urinary sodium and creatinine can document compliance**
 - **Patients excreting more than 78 meq of sodium per day should lose weight**
 - **Urinary Cr. Males > 15 mg/kg/d; Female >10 mg/kg/d**
- **Spot urinary Na/K ratio > 1.0 correlates with sodium excretion > 78 meq with a 90% sensitivity**

Refractory Ascites: Evaluation

- **Ultrasound or CT to rule out hepatocellular carcinoma or portal vein thrombosis**
- **Evaluate for liver transplant**
 - **Progression to refractory ascites is a marker of irreversible end-stage liver disease**
 - **The six-month survival is 50% and one year survival 25%**
- **High risk of hepatorenal syndrome**

Refractory Ascites: Treatment

- Repeated large volume paracentesis (LVP)
- Transjugular intrahepatic porto-systemic stent-shunt
- Liver transplantation
- Peritoneo-Venous Shunt (PVS) (historical interest only)



Large-Volume Paracentesis (LVP) vs. Diuretics in Uncomplicated Tense Ascites

LVP

- **Faster resolution of ascites (of particular relevance in hospitalized patients)**
- **Fewer complications**

Diuretics

- **General applicability**
- **Ease of administration**
- **Low cost**

Refractory Ascites: LVP

- **LVP proven effective and relatively safe in randomized controlled trials**
 - **Improved patient comfort/breathing**
 - **Reduces hepatic venous pressure gradient, intravariceal pressure and variceal wall tension**
 - **Improves gastric accommodation and caloric intake**
 - **May reduce incidence of SBP and variceal bleeding**

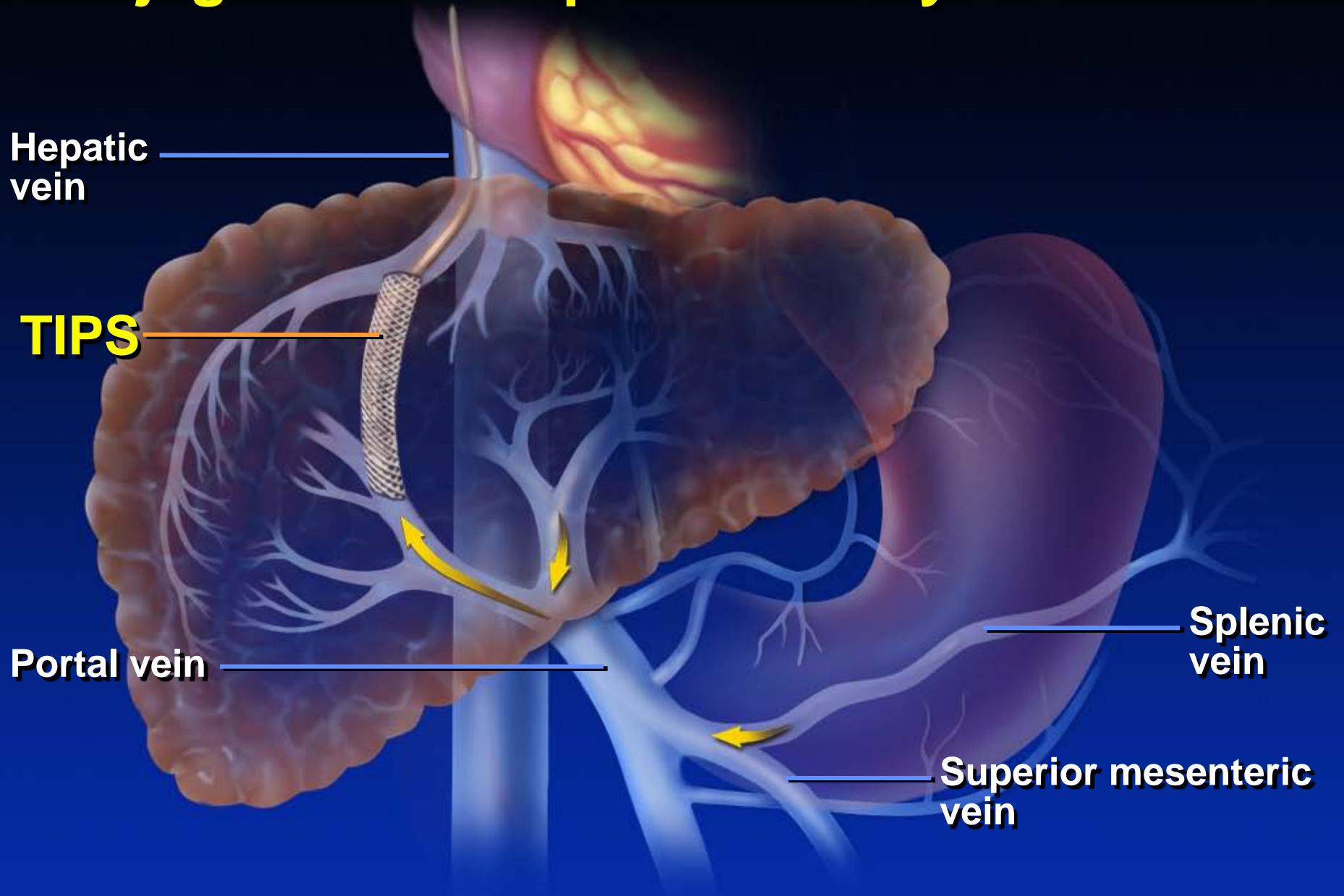
Refractory Ascites: LVP

- **LVP can be done in the out-patient setting**
- **The risk of major complications (bleeding, bowel perforation, infection) is 0.2% and death <0.01%**
- **The major risk factor for bleeding was Child-Pugh score, but not platelets, INR, or operator experience**

Refractory Ascites: LVP

- The need for colloid replacement remains controversial
- Removal of up to 5 liters of fluid does not appear to require colloid replacement
- Albumin infusion recommended for larger paracentesis volumes: 6-8 grams of albumin per liter removed
- Survival benefit and cost-effectiveness of albumin replacement not established
- Routine ascites culture not indicated unless increases PMN noted

Transjugular Intrahepatic Portosystemic Shunt



Refractory Ascites: TIPS

- **Benefits:**
 - **Reduced portal pressure**
 - **Rapid reduction or elimination of ascites**
 - **Reduction or cessation of diuretic therapy**
 - **Improved renal function**
 - **Improved nutritional status**

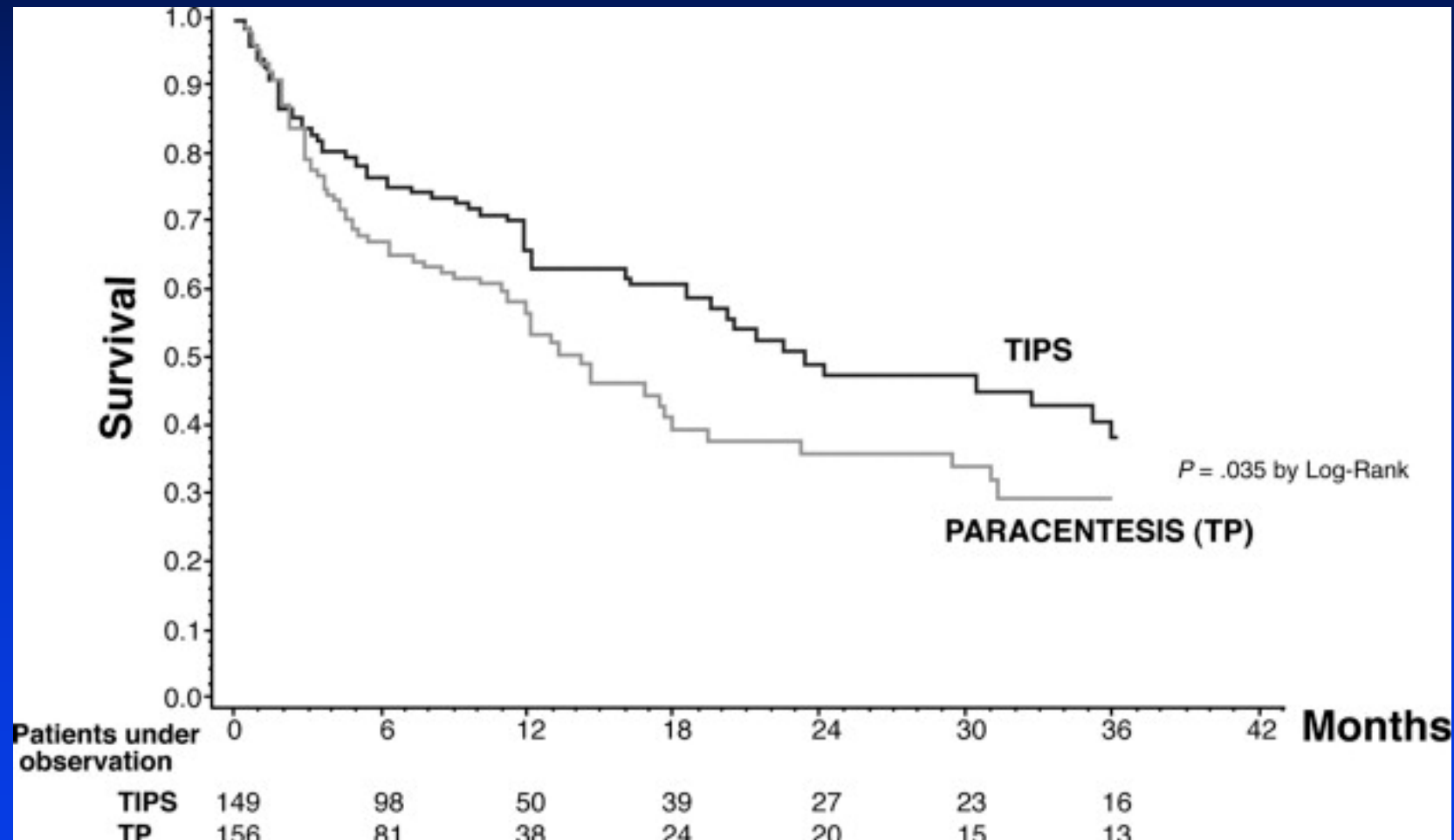
Refractory Ascites: TIPS vs LVP

- 2005 meta-analysis of 5 trials comparing TIPS to LVP for refractory ascites
- TIPS gave superior ascites control (62% vs 24%) but higher rates of hepatic encephalopathy (40% vs 22%)
- No statistical difference in 2 year survival (25-35%)
- TIPS more expensive and shunt stenosis common

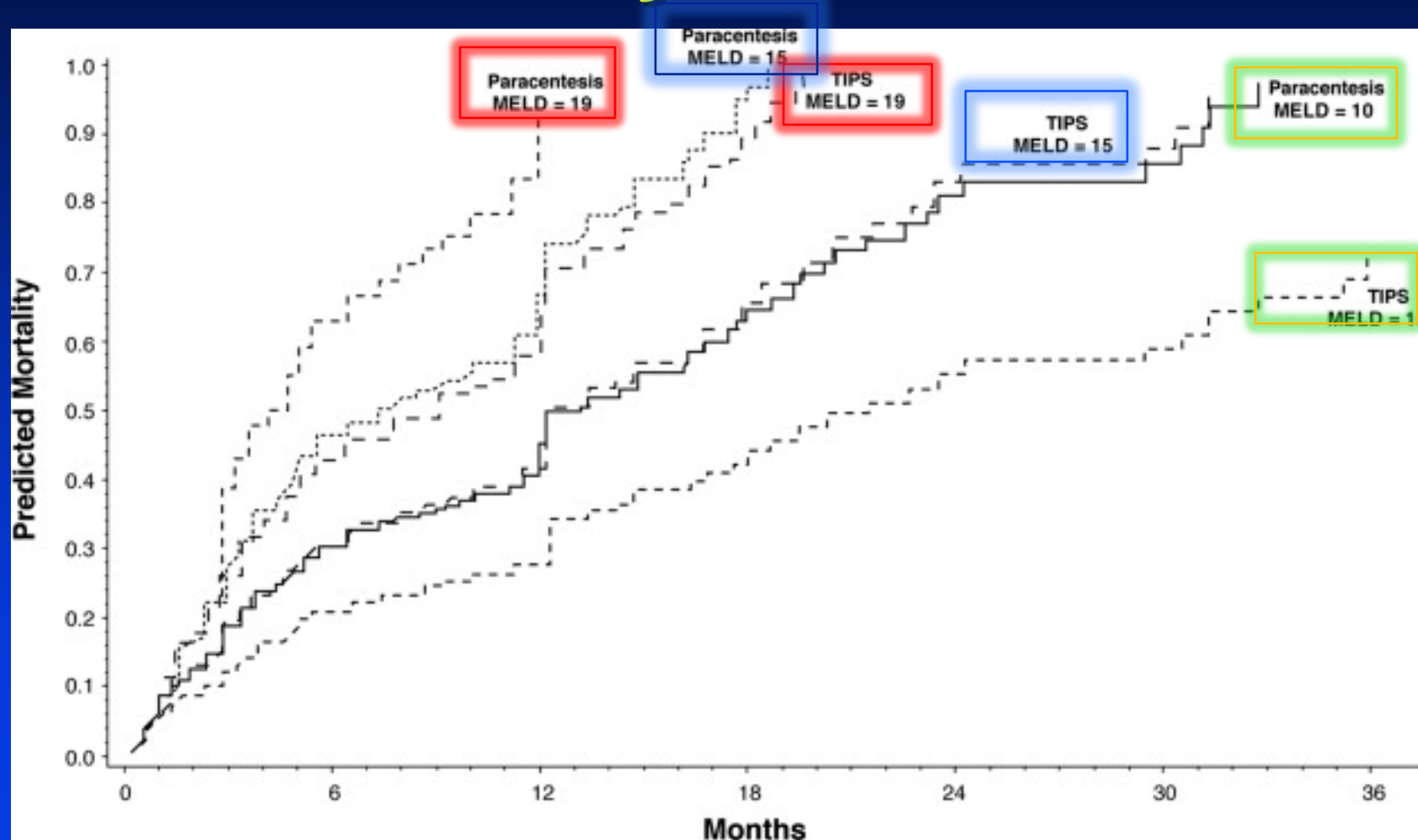
Refractory Ascites: TIPS vs LVP

- 2007 meta-analysis of 305 patients with RA randomized to TIPS vs LVP
- TIPS associated with significantly improved transplant-free survival, superior control of tense ascites, lower incidence of SBP, hepatorenal syndrome, and GI bleeding
- The average number of hepatic encephalopathy events was significantly higher with TIPS but the cumulative probability of the first HE episode similar

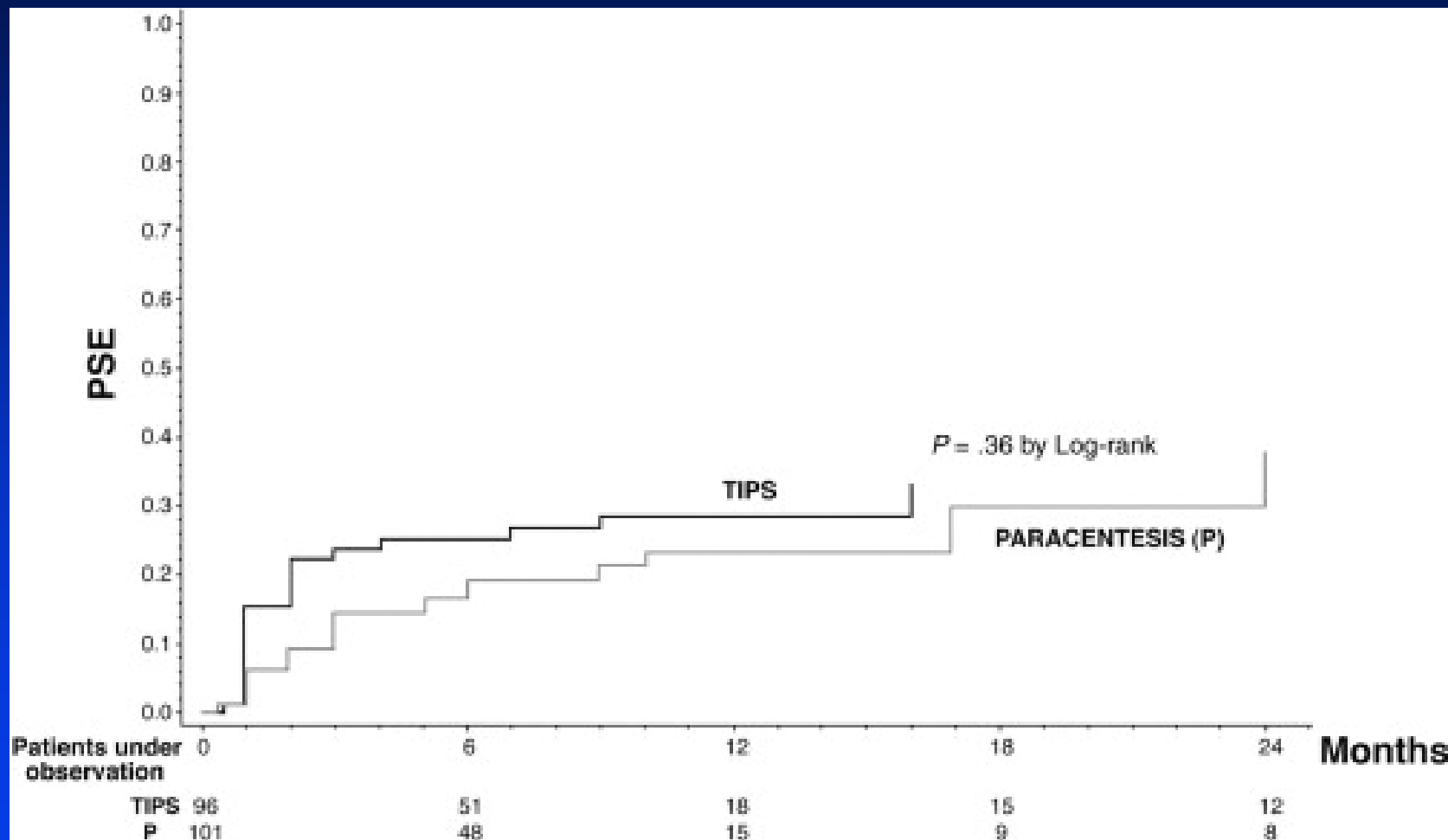
Cumulative Probability of Transplant Free Survival



Estimated Probability of Death Stratified by MELD Score



Cumulative Probability of at Least One Episode of HE



Gastroenterology 2007;133:825

Refractory Ascites: TIPS vs LVP

- Predictors of poor outcome with TIPS
 - Age >65
 - CHF: EF < 60% (most cirrhotics have EF 70-75%)
 - Child-Pugh score >12
 - Preexisting hepatic encephalopathy
 - Severe pulmonary hypertension

Refractory Ascites: TIPS vs LVP

- Repeated therapeutic LVP, with or without albumin infusion, is the initial treatment of choice for refractory ascites
- Consider TIPS in carefully selected patients
 - Require > three LVP/month
 - Loculated ascites
 - Childs-Pugh score <12
- TIPS is best avoided if the patient is likely to receive a liver transplant in the near future.

Contraindications to Placement of a TIPS†

Absolute

Primary prevention of variceal bleeding
Congestive heart failure
Multiple hepatic cysts
Uncontrolled systemic infection or sepsis
Unrelieved biliary obstruction
Severe pulmonary hypertension

Relative

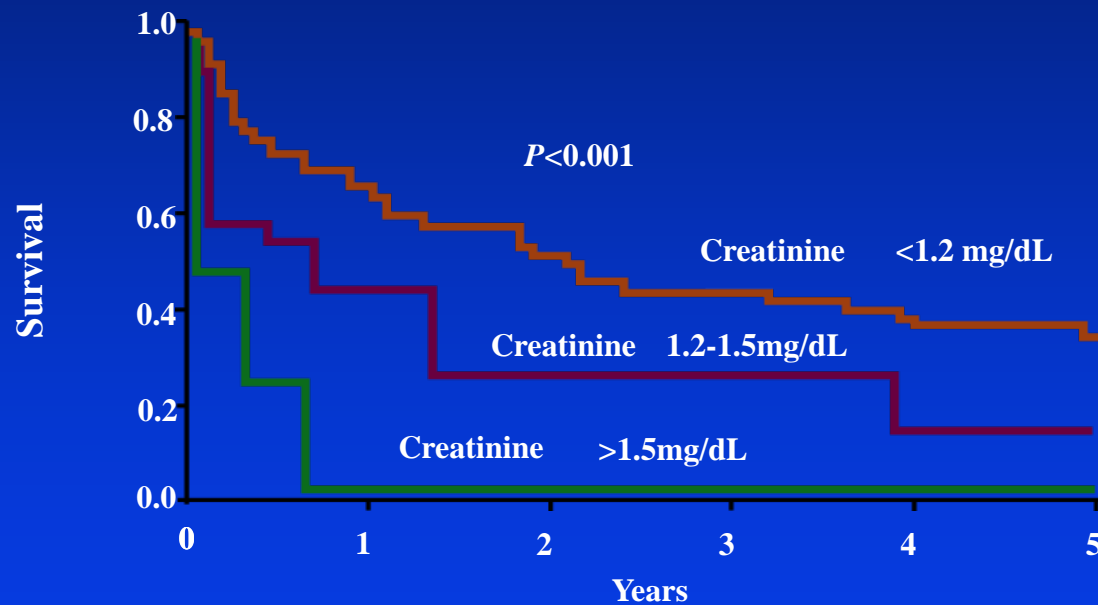
Hepatoma, especially if central
Obstruction of all hepatic veins
Portal vein thrombosis
Severe coagulopathy (INR >5)
Thrombocytopenia of less than 20,000/cm³
Moderate pulmonary hypertension

† Boyer, TD and Haskal, ZJ. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. Hepatology 2005; 41 :386.

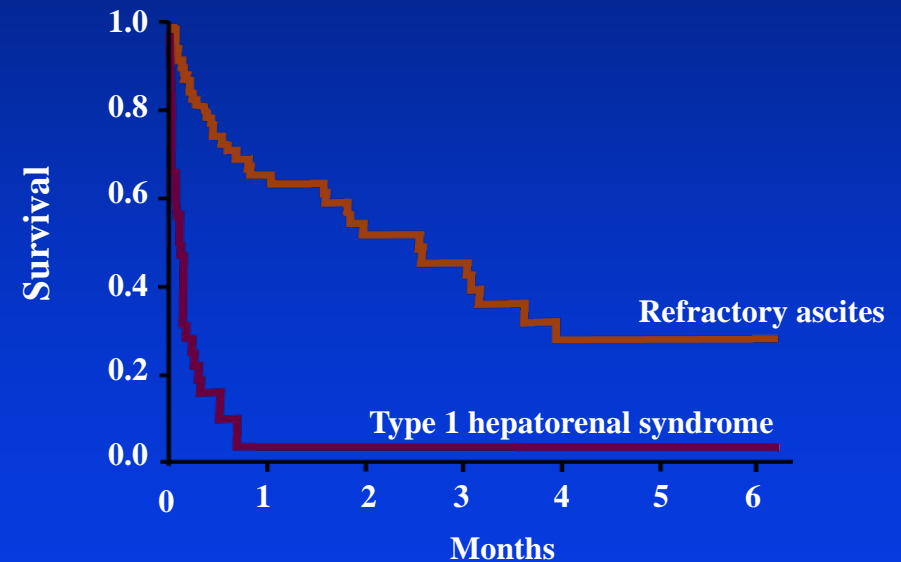
Hepatorenal Syndrome

Survival is Decreased with Renal Dysfunction

Survival in Cirrhosis Based on Level of Renal Dysfunction



Survival Among Patients With Cirrhosis and Hepatorenal Syndrome



Prevention of Acute Renal Injury in Cirrhotics

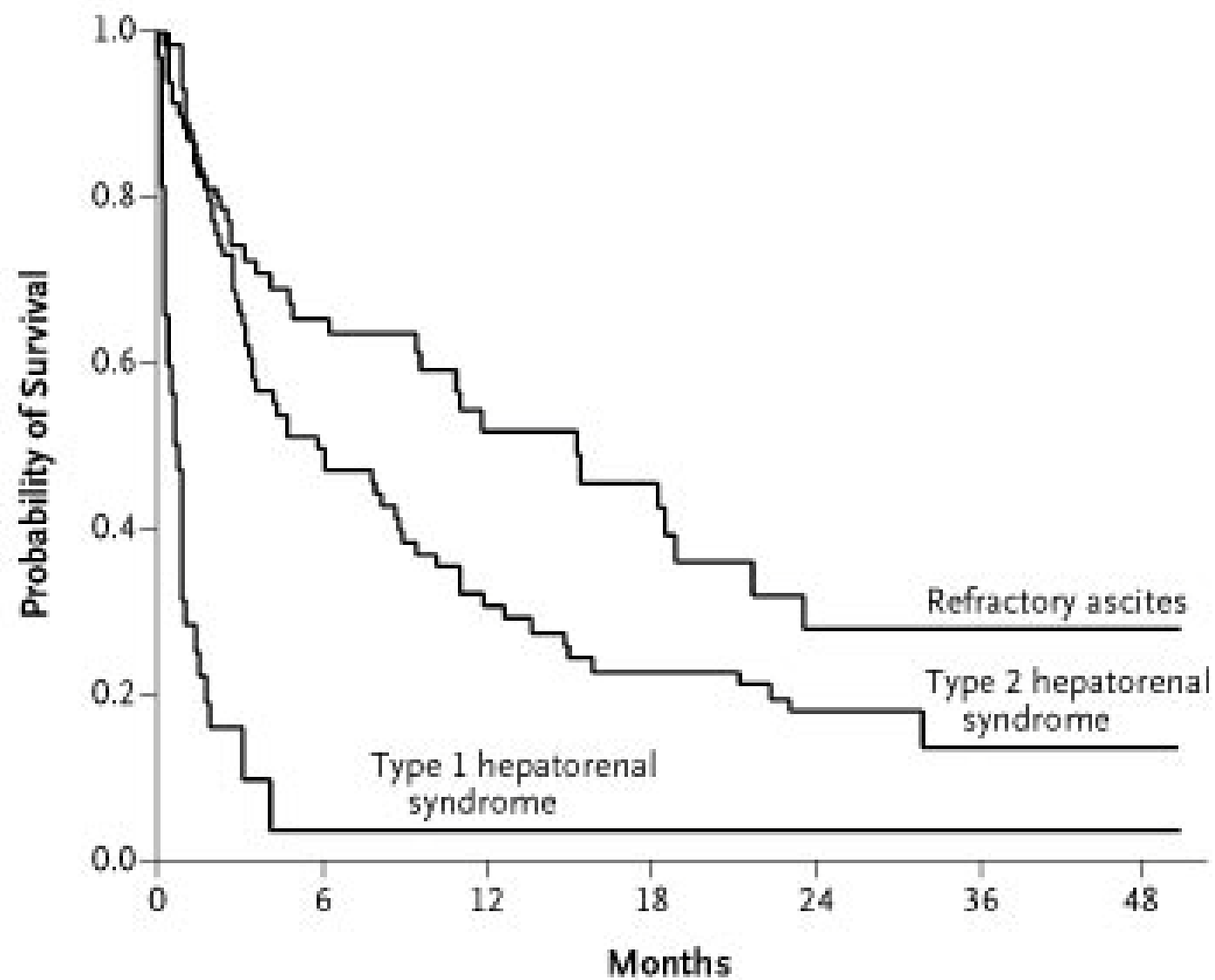
- **Avoid aminoglycoside antibiotic**
 - **10-fold increase renal toxicity**
- **NO NSAIDs**
- **Avoid I.V. contrast or hydrate and use NAC**
- **Frequent monitoring of renal function in cirrhotic patient with ascites is essential**
- **Patient instruction on use of diuretics, lactulose, antibiotics**

Hepatorenal Syndrome

- **Acute renal failure due to advanced liver disease**
 - **Cirrhosis**
 - **Severe Alcoholic Hepatitis**
 - **Fulminant Hepatic Failure**
- **Incidence 10% in patients hospitalized with cirrhotic ascites**
- **In decompensated cirrhotics, the incidence of HRS is 8-20% per year**

Hepatorenal Syndrome

- Type 1 HRS
 - Rapid and progressive renal insufficiency
 - Most commonly precipitated by SBP
 - Median survival 2 week
- Type 2 HRS
 - Moderate and more gradual reduction in GFR
 - Often associated with diuretic resistant ascites
 - Medial survival 3-6 months



HRS Diagnostic Criteria

- **Diagnosis of exclusion**
- **Low GFR: Creatinine > 1.5 or GFR < 40 ml/min, that progresses over days to weeks**
- **Absence of shock, unresolved bacterial infection, fluid losses or nephrotoxic medications**
- **No sustained improvement in renal function after diuretic withdrawal and plasma volume expansion with 1.5 liters of volume expander**

HRS Diagnostic Tests

- Paracentesis
 - Occult SBP may present as HRS
 - HRS complicates approximately 25% of SBP
- Renal ultrasound
- Urinalysis
 - Urine sodium <10 meq/ml
 - Urine osm greater than plasma
 - Urine volume less than 500 cc/day
 - Urine protein less than 500 mg/day

HRS : Consultations

- **Hepatologist:**
 - **Liver transplant evaluation**
- **Nephrologist**
 - **Dialysis considered only in potential transplant candidates**
- **Interventional radiologist**
 - **TIPS**

Table 4. Recommendations for Treatment with Vasoconstrictors in Patients with the Hepatorenal Syndrome.

Recommendation	Reference
Administration of one of the following drugs or drug combinations	
Norepinephrine (0.5–3.0 mg/hr intravenously)	Duvoux et al. ⁴⁸
Midodrine (7.5 mg orally three times daily, increased to 12.5 mg three times daily if needed) in combination with octreotide (100 µg subcutaneously three times daily, increased to 200 µg three times daily if needed)	Angeli et al. ⁴⁹
Terlipressin (0.5–2.0 mg intravenously every 4–12 hr)*	Uriz et al., ⁵⁰ Moreau et al., ⁵¹ Mulkay et al., ⁵² Ortega et al. ⁵³
Concomitant administration of albumin (1 g/kg intravenously on day 1, followed by 20–40 g daily)	Duvoux et al., ⁴⁸ Angeli et al., ⁴⁹ Uriz et al., ⁵⁰ Ortega et al. ⁵³
Duration of therapy: 5–15 days	
End point: reduction of serum creatinine concentration to <1.5 mg/dl†	

* Terlipressin is not available in some countries, including the United States.

† To convert the value for creatinine to micromoles per liter, multiply by 88.4.

HRS : Drug Treatment

- **Midodrine:**
 - Selective alpha-1 adrenergic agonist
 - Systemic vasoconstrictor
- **Octreotide:**
 - Inhibitor of endogenous vasodilator release
- **Midodrine 7.5-12.5 mg tid plus octreotide 100-200 mcg tid with daily albumin infusion associated with reduced mortality in one uncontrolled trial**

HRS : TIPS

- No controlled trial of TIPS in HRS
- Patients treated with TIPS for refractory ascites show improved renal function have a lower incidence of HRS
- In one series, TIPS associated with improved GRF and 20% one year survival for Type 1 HRS and 45% survival for Type 2 ([Gut 2000;47:288](#))
- At this time TIPS for HRS is considered investigational and not recommended by the AASLD pending results of controlled trials